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ANNUAL REPORT OF PROGRAM ACTIVITIES, NATIONAL INSTITUTE OF MENTAL HEALTH FISCAL YEAR 1974 VOLUME I

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

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ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF MENTAL HEALTH

Fiscal Year 1974

Volume I

ANNUAL REPORT of program activities

MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM -
Division of Clinical and Behavioral Research, and
Division of Biological and Biochemical Research

US NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1973 - June 30, 1974

VOLUME I

Summary Statements

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MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM -
Division of Clinical and Behavioral Research, and
Division of Biological and Biochemical Research
NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1973 - June 30, 1974

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ANNUAL REPORT
of the
DIRECTOR, MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM
NATIONAL INSTITUTE OF MENTAL HEALTH
July 1, 1973 - June 30, 1974

John C. Eberhart, Ph.D.

In this brief annual report, I want to comment on some of the events of the past year that affect our research program and have an impact on the productivity of our scientists. The important part of the program's annual report is, of course, the story told by the Laboratory Chiefs in the summaries to follow of the scientific work accomplished and the new discoveries of method and substance. I shall not further summarize those accounts. It is clear that research has continued at a high level, and the reasons for this are equally clear--the quality of our scientists, and the generally excellent facilities and research environment in which they work. Some of the matters I will discuss are handicaps, others are assets, but all deserve some comment.

During the past seven years the NIMH has consecutively been a component of the National Institutes of Health, an independent Bureau, a component of the Health Services and Mental Health Administration, again a part of the NIH, and finally a component of the Alcoholism, Drug Abuse, and Mental Health Administration. The year just past might be called the year of ADAMHA. Though the NIMH rejoined the NIH on July 1, 1973, that happy status lasted just until September 25, 1973, on which date the Department created a new Agency called ADAMHA as a redesignation of what had up to that date been NIMH. In the same action, the Secretary created a new and smaller NIMH, composed mostly of the traditional operating mental health Divisions. Thus our present parent Agency ADAMHA now includes the new and smaller NIMH, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse. In seven years, the NIMH has thus had five different organizational statuses. It is not surprising that members of the staff sometimes don't know what to call home.

Throughout this entire period, the NIMH Intramural Research Program has continued its close association, both geographic and spiritual, with the NIH. Under the joint administrative supervision of the NIH, our laboratories have operated as if they were a part of the NIH, following the same policies and procedures, adhering to the same standards, and participating in the same intellectual and scientific climate. Dr. John Sherman, Deputy Director of NIH, in a letter written a year ago commented on "the unique cooperative management relationship which has existed for the past decade between NIH and the NIMH Intramural Research Program." He mentioned also the "remarkable success of this administrative arrangement which has survived many stresses and yielded international recognition..." At least half the credit for this remarkable arrangement, and I think more than half, is due to that remarkable group of men who have governed the NIH during the past decade.

Drs. James Shannon and G. Burroughs Mider have been mentioned in earlier reports, and their places in NIH history are deep and permanent. But their successors, Drs. Robert Marston, Robert Berliner, John Sherman, and Carl Leventhal, were equally fine and have maintained the stature of the NIH under increasing budgetary and political difficulties. I regret to record the fact that the NIH has had major personnel losses during the past year: Dr. Berliner, who resigned to become Dean of the Yale University College of Medicine; Dr. John Sherman, who resigned to become Vice-President of the Association of American Medical Colleges; and Dr. Carl Leventhal, who resigned as Special Assistant to Dr. Berliner to join the staff of the Food and Drug Administration. (Dr. Marston left NIH in F.Y. 1973.) When one adds to this list the resignations or retirements this year of four Scientific Directors (Dr. Donald Frederickson, NHLI; Dr. Henry Wagner, NINDS; Dr. Richard Greulich, NIDR; and Dr. Gordon Zubrod, NCI) and the retirement also of Mr. Jack Sangster, Director of Personnel Management, NIH, it is clear that the NIH, and the NIMH-IRP, have been badly hit.

Before leaving the subject of the NIH, I want to say that we have welcomed the new Director, Dr. Robert Stone, the new Deputy Director for Science, Dr. DeWitt Stetten, Jr., an old friend, and the new Assistant Director for Intramural Affairs, Dr. Philip Chen. We look forward to the same kinds of satisfying relationships that we have had with their predecessors.

Our last change in organizational status--inclusion in ADAMHA--had the unfortunate side effect of abolishing the Intramural Research Program, as an entity, which is less drastic than it sounds. In December 1973, during the process of completing the organization charts and functional statements of ADAMHA, the Office of the Assistant Secretary for Administration objected to the existence of an "Intramural Research Program" as a layer in between the NIMH (a "Bureau") and three intramural Divisions on the grounds that the Department's nomenclature rule for organizational structure had no place for such a layer. Though we pointed out with vigor in every forum open to us that a line structure was needed to run three research divisions, that it had operated effectively and efficiently for eight years, and that both the Research Task Force and a special Committee to Study the Organization of Intramural Research Programs of ADAMHA were then studying aspects of NIMH research, our protests were not heeded. The new organization chart for ADAMHA came out with no "Intramural Research Program" on it; instead, a new unit called "Office of Research Coordination" was drawn in showing a dotted-line relationship to each of the three Intramural Divisions and the same dotted line to the Division of Extramural Research Programs. The "ORC" was given all the personnel of the IRP (which included the entire Section on Technical Development), and the IRP functional statement was reprinted for the ORC for which it was entirely inappropriate.

The only concession we could get was word from the Assistant Secretary for Health that we need not implement the new organization until the report of the Research Task Force and that of the Committee to Study the Organization of Intramural Research Programs in ADAMHA were available for study, at which time the matter could be reopened. The Research Task Force report is virtually complete and does not directly address the structural issue in

question. The Committee report is complete and was transmitted to Dr. Roger Egeberg, Interim Administrator of ADAMHA, on June 3, 1974. In my memorandum of that date transmitting the report I said, "I would like to emphasize two of the recommendations that are of especial importance to me at this time. The first is Recommendation 4--that the NIMH Intramural Research Program, which was converted into an 'Office of Research Coordination' by the Office of the Secretary, be reestablished promptly as a line structure to manage the three intramural research Divisions in NIMH. The change was originally made to secure uniformity in nomenclature throughout the Department; in response to our protests we were told that the change need not be implemented until the present Committee had had a chance to study the situation and make its recommendations. The Committee feels unanimously and strongly that the original structure worked well, that the proposed 'Office of Research Coordination' cannot satisfactorily administer these programs, and that the NIMH 'Intramural Research Program' should promptly be restored as an exception to the Department's nomenclatural rules. Since this action requires Departmental concurrence, I am enclosing a draft memorandum directed to the Assistant Secretary for Health."

I hope that the good sense of our position will secure for us an exception to the Department's nomenclature rule, preferably on the basis of merit, but if necessary on the grandfather principle.

Since the Committee has come up, I would like to characterize its work briefly. It was set up in response to questions raised in the Administrator's office about how intramural research should be organized and managed in the new agency, ADAMHA. The Committee, appointed by Dr. Egeberg, included Drs. Floyd Bloom, William Bunney, Robert Cohen (all from NIMH), Mr. John Deering (NIAAA), Dr. William Pollin (NIDA), and me as Chairman; Mr. Daniel Rice served as Executive Secretary. The Committee met ten times beginning January 9, 1974, three of the meetings being with Dr. Egeberg, and one meeting each with Drs. Brown (NIMH), Chafetz (NIAAA), and Dupont (NIDA). The Committee recommended that (1) ADAMHA foster and support a balanced national effort of research and research training in the scientific disciplines relevant to its mission, (2) ADAMHA maintain and support a strong intramural research program in each of its three Institutes as a national resource, (3) independent intramural research programs in each Institute with active encouragement of ample opportunity for cooperation across Institute lines at all levels, (4) the line position for direction of mental health intramural research be reestablished without delay including the necessary administrative staff for proper functioning, (5) a joint monthly meeting of Scientific Directors of each Institute with the Administrator and that the determination of the need for a full-time staff officer for research at the ADAMHA level flow from the experience of these meetings, and (6) the Committee be assigned the further task of gathering facts and paving the way for a feasibility study on the location and construction of a single facility to house all ADAMHA intramural research programs.

As I reread what I have written, it occurs to me that it is probably a principle of bureaucracy that large organizations devote much energy and manpower to the self-sustaining functions of organizational life. These would

include perfecting organizational structure, reorganizing for greater "efficiency," communication among the parts, and other selected matters. All are necessary to some extent, but they can become absorbing ends in themselves and overshadow the true goals of the organization. The Intramural Research Program exists only to discover new knowledge--knowledge that will aid our understanding and control of the mental disorders, and knowledge that will expand our mastery of the sciences from which useful future applications must come. We have tried to concentrate the resources of the Intramural Program on science, rather than on bureaucracy, and have staffed the Program thinly at the administrative level to save positions for use at the bench and the bedside.

I say these things in my own defense because what I have talked about up to now has been mostly bureaucracy, rather than science, and most of what I have yet to report is also bureaucracy. During a good part of the year, we (Dr. Cohen and I) were trying to reorganize the Intramural Research Program. The effort merits some comment because the issue touches on a number of aspects of the IRP as a social organization.

I reported a year ago that Laboratory and Branch Chiefs had met for two days at Cacapon Lodge to discuss the impact on the Program of the declining budget and some issues of reorganization. The principle question addressed in that meeting was, "Does the Intramural Program have too many independent investigators for its present level of support?" The consensus answer was yes, IRP does have too many independent investigators at present support levels, but there was no consensus on what to do about it.

Beginning in the fall of 1973, a number of discussions were held by the Division Directors and Administrative Officers with the Laboratory Chiefs as a whole and with selected numbers of that group. The discussion process was far from smooth, in part it seemed to me because both ends and means were unclear. The Federal system provides no ready means for reducing the number of independent investigators. Even the "reduction in force" procedure, which we were not free to use, is an inefficient means of preserving the best. To some of us it seemed that some reorganization of the IRP might be an indirect step in that direction and might have direct benefits in the way of bringing closer together those working on related problems or with related methods. We finally proposed to the Laboratory Chiefs that (1) IRP scientists be divided into five or six subject-matter groupings, ignoring existing Laboratory lines; (2) each group select a chairman; (3) each group work out a statement of the kinds of research that it would recommend for that group; (4) on the basis of these statements, decisions be made as to a new arrangement of Laboratories and Branches which might provide a better focus for research effort and resources.

Objections of a surprisingly vigorous sort were made to these proposals, for quite different reasons. I suppose that if a common thread could be said to run through the objections, it would be that the proposed procedure seemed to many a waste of time. Some of the Laboratory Chiefs had no interest in seeing their laboratories reorganized and did not want to go through what they regarded as a kind of groupy academic exercise aimed at reorganization. Some

conceded that some reorganization might not be bad, but that if the Directors of the Program wanted it reorganized they should design it themselves.

The opposition finally appeared to be sufficiently deep seated in DBBR and DSMHR that I withdrew the proposal for those Divisions. The DCBR Laboratory Chiefs were interested in some further discussions, and Dr. Cohen convened them for a series of additional meetings. Tentative proposals for some reorganization have since been generally agreed upon for DCBR, although they are not yet implemented. Dr. Cohen will probably review those steps in his Annual Report a year from now.

It sometimes seems to me that it is only because I spend virtually all my time in these "bureaucratic" matters that the scientists in the Program are left fairly free to do science. Even then, however, it is my impression that administrative (bureaucratic?) matters make larger inroads in scientists' time each year. This year DSMHR scientists have spent three half-days reviewing and demonstrating their work to the Administrator of ADAMHA, the Assistant Secretary for Health, and an OMB staff examiner; Laboratory Chiefs in the Bethesda Divisions have spent two half-days doing so. Two Laboratory Chiefs (Drs. MacLean and Snyder) have taken most of a morning to review their research fields for the Secretary's Wednesday morning conference. These activities, and others like them, are part of our effort, willingly made, to make the Program and its needs better known inside the Government and thus to facilitate budgetary support. These problems are more difficult to solve when there are rapid organizational changes and many changes in upper level Departmental and Executive Office personnel. They are made more difficult also by any decrease in the general high regard for science, either in society as a whole or in the Government, of which there have been a number of signs during the past few years.

In general, "non-happenings" should be omitted from Annual Reports, unless something is to be learned by recording one. I'm not sure whether that rule applies to our spring 1974 budget crisis, but it may be worth a paragraph.

When the Administration's final version of the F.Y. 1975 budget became available (in February of this year), we learned that it imposed an end-of-year personnel ceiling on the NIMH that was 184 positions below its actual employment at that time. In effect, the NIMH would have to reduce its staff by that amount by June 30, 1974. This requirement was imposed despite the strongest possible objections from the NIMH Director. Furthermore, the Department required that the NIMH specify in detail how it proposed to reduce its staff to meet the lower ceiling. We know that a budget does not become binding until passage of an appropriation bill containing it, and thus that the dire fate in store for us could be prevented by action of the Congress, but no one can be sure of Congressional action, and we had to prepare for the worst.

The impact of this budgetary cut on the Intramural Research Program became clear after the Director of NIMH divided up the lost positions among the offices and divisions. We were to lose our existing 25 vacancies, as were other divisions to lose theirs, and in addition would have to lose 33 more

filled positions, for a total loss of 58 budgeted positions from our authorized total of 378, a loss of 15 percent. (At that, the Intramural Program was assessed at a lower rate than most other parts of the Institute.)

In a series of agonizing discussions between the Intramural Division Directors and Administrative Officers, and in the face of the greatest reluctance on my part to specify in advance how we would absorb a cut of 58 positions, we finally proposed a plan for discontinuing enough Laboratories to eliminate 58 positions by a "reduction in force." I did not disclose the plan to members of our staff because there was no certainty that we would have to follow it; I did not think a workable plan could be drawn up in the absence of the certain knowledge that it would have to be implemented; and I knew it would be a blow to any Laboratory, Section, or individual on the list. The nature of the crisis was fully explained to the Laboratory Chiefs, and they were aware that we had to submit a plan for taking cuts if the proposed budget became a reality.

The threat of cuts was very real, and although it was not the first fiscal danger we have encountered, its impact was considerable. Since the same cuts were not being threatened for NIH, a few of our staff concluded that the IRP would be better off as a part of NIH, and in one way or another they urged that such a transfer be made. I felt that a transfer of the NIMH-IRP out of the NIMH and into the NIH would be not only undesirable but quite impossible, even though I favored including the NIMH as a whole in the NIH. In a final Laboratory Chiefs' meeting attended by Dr. Bertram Brown, most views on this transfer issue were stated candidly and rather bluntly. It was my impression that active seeking for a transfer of IRP only did not long continue.

The epilogue is that, after considerable public and Congressional protest, the Department decided not to institute a reduction in force, and finally the 1974 personnel ceilings were restored with minor exceptions. As of this writing, the 1975 appropriation bill has not been passed, but action taken so far suggests that we will receive only slightly less than we received in F.Y. 1974.

To turn now to several other matters in the year just past, among other valuable efforts during the year have been those by staff and administration to make our Equal Employment Opportunity program as successful as possible. Because we have not been able to find many acceptable minority candidates for Staff Fellow vacancies, we decided in December 1973 to reserve six positions over a two-year period for appointment of minority Staff Fellows. The candidates would be expected to meet ordinary qualification standards, but the positions would not come from the Laboratory's allotment. By year's end, despite recruiting efforts by several Laboratories, no appointments had been made. We hope that we will fare better in the coming year. The EEO program was kept going by the good work of the EEO Council, chaired successively by Harry K. Thompson and Erskine Davis, and by Dr. Allen Dittmann, Deputy EEO Officer. We are grateful to all of them, and we are sorry that Dr. Dittmann has announced his departure, as of September 1, for the faculty of the University of Maryland.

I have been increasingly impressed over the three years of the IRP "satellite" Personnel Office with the value to a program like ours of a personnel staff who are (1) close physically to the research operation, (2) identified with the Program, and (3) able, competent, and devoted. Although our satellite office is handicapped by lack of adequate authority and autonomy, still the group under Mrs. Margaret Braymer has done an outstanding job in looking after the needs both of the Program and of the staff members. Mrs. Braymer herself has been an important and valued member of our staff, even though officially she is a member of the Parklawn Personnel Office. I am grateful for her many contributions to the Program and for the opportunity to learn from her how well personnel work can be performed.

The NIMH Research Task Force has by now (July 6, 1974) completed almost all of its work, and a draft report has semi-officially been presented to Dr. Brown. Editing of two or three more chapters remains to be done, but the shape of the report is fairly clear. It will be a printed volume of more than 300 pages, with a summary first chapter plus 17 others. Most arguments within the Coordinating Committee have been over the details of Chapter 16, on "Organizational and Administrative Issues," because, while words are not always permanent, administrative structures tend to persist, and thus it is better to get them right.

We invited the Board of Scientific Counselors to review the Research Task Force report at the March 29-30, 1974, meeting. Unfortunately, only about two-thirds of the report was in draft form in time to mail to Board members, with some other chapters available to hand out at the meeting. Several members of the Task Force staff and chairmen of Task Force committees met with the Board to summarize sections of the report and to contribute to the discussions. Those participating included Drs. Floyd Bloom, Donald Boomer, Patricia Goldman, Martin Katz, Melvin Kohn, Morris Parloff, Morris Rosenberg, Julius Segal, and Marian Yarrow. Since a two-day meeting did not provide time to review the entire report, we limited the agenda to the four chapters on basic research ("Biological Processes," "Psychological Processes," and "Social and Cultural Processes") and to four others ("Social Problems," "Treatment of Mental Disorders," "Mental Illness and Behavior Disorders," and "Organizational and Administrative Considerations"). There was a good deal of interest shown by the Board in the chapters on basic research and some discussion of those matters followed, but the issue which received the most attention was the question of "peer review" of intramural research. More aspects of this complicated subject were opened up than were settled.

Present for the March meeting were Drs. Eugene Bliss, Walle Nauta, Eleanor Sheldon, and Robert Stubblefield. One new member had been appointed to the Board but was unable to be present: Dr. Eleanor Gibson, Professor of Psychology, Cornell University.

At the fall meeting of the Board (October 26-27, 1973), we presented the research program of the Child Research Branch, in part because it had not recently been reviewed, and in part because it is in its terminal phases, with the large task of analyzing and interpreting the longitudinal data facing it. To assist the Board in this review, we invited Dr. Robert R. Sears of Stanford

University and Dr. William Kessen of Yale University to serve as special consultants, and both attended the meeting and made valuable contributions. Dr. Bliss, Chairman of the Board, prepared a report of the Board's review of the Child Research Branch, the first of what I hope will be many others prepared by the Board rather than by the staff.

There appears to be increasing sentiment among both administration and scientific staff of the IRP for more critical and systematic review and evaluation of the research of laboratories and individuals. I hope that the Board, bolstered by ad hoc consultants as needed, can handle a good deal of this problem. There will remain other aspects of what is called "peer review" in the extramural program, and we will be dealing with these in the coming year.

We regret the loss of Dr. Bliss from the Board of Scientific Counselors--his term expired on June 30, 1974--but we are glad that Dr. Stubblefield has agreed to become the new Chairman. At our next meeting, we will welcome another new member, Dr. Albert Lehninger, Professor and Chairman of the Department of Physiological Chemistry at the Johns Hopkins University School of Medicine.

During the past year a permanent successor to Mr. James Bryan, former Chief of the Section on Technical Development, was chosen. He is Dr. Theodore R. Colburn, who has been with the Section since 1966. We are delighted that he has agreed to take on this challenging job. At the same time, we very much regret the loss by retirement on June 30, 1974, of Mr. Daniel G. Rice, who has been a fine Information Officer for the Intramural Research Program for the past four years.

No member of our staff was on a foreign work study assignment this year. Two members had been recommended, however, but both found it necessary to change their plans before decisions were reached.

Finally, may I say a word in appreciation of the work of the NIMH Assembly of Scientists during the past year. Three successive Presidents of the Assembly have been actively involved in serious study of various aspects of the Intramural Research Program, and reports which they and their Council committee members have submitted to us have been stimulating and helpful. The Presidents have been Drs. Melvin Kohn, Josephine Semmes, and Patricia Goldman. In addition, Drs. Audrey Stone and Elliot Liebow have been members of a committee that met frequently with Dr. Cohen and me to go over issues of program governance, quality control of intramural research, scientist participation in selection of program leaders, and a number of others. We have not always agreed with Assembly positions on issues, but even where we have disagreed their arguments have been persuasive and their perceptions insightful. I have learned much from them, and I hope they continue their interest in improving intramural research, both for the sake of the people in the Program and for the sake of the new knowledge whose pursuit justifies our existence.

Annual Report of the
Director, Division of Clinical and Behavioral Research
National Institute of Mental Health

July 1, 1973 - June 30, 1974

Robert A. Cohen, M.D., Ph.D.

The past year has been in many ways the most difficult since the founding of this research program. Our pleasure at the return of the National Institute of Mental Health to our family of origin, the National Institutes of Health, was short-lived. The subsequent establishment of the Alcohol, Drug Abuse and Mental Health Administration has thus far had minimal direct impact on the Intramural Research Program, but there is an atmosphere of instability and uncertainty about the future which compounds the forebodings engendered by the criticisms and generally diminished acceptance of basic research. Many of us may still believe that we are indeed engaged in an important or even noble enterprise, but it is easier to sustain that attitude when it is reinforced by the public interest and support we once enjoyed. We had rested secure in the expectation that if our program continued reasonably productive we would continue to enjoy undiminished resources. In fact, with the passage of time our goals had become somewhat more modest than they had been in earlier years; we no longer even attempted to cover so broad a field of investigations relevant to increased understanding of behavior. As opportunities for change in program direction were afforded by the completion of various projects and/or the resignation or retirement of members of the staff, we had concentrated our efforts on increasing the strength of those elements of our program which we believed could make the best immediate use of the resources and the setting at our command. Obviously, not every project lay in an area of rapidly increasing knowledge nor did it result in the breaking of new ground, but it had seemed inconceivable that the government would ever curtail a program as strong as ours, working so successfully on issues so important to mankind.

It has been, to say the least, a blow to some that the Intramural Research Program should have been required to participate in the proposed reductions in force of the entire National Institute of Mental Health -- so much so that several scientists even wished to dissociate themselves and us from the Institute. They believed that research is surely dear to the hearts of the nation and to its congressional leaders. In his very perceptive essay on Science and Social Purpose, Caryl Haskins has placed some of these restrictive pressures in broader perspective. It may have been true that the primary targets in the dissolution of the original National Institute of Mental Health were its training and service programs, but as Haskins points out this is also a time of disenchantment with all research -- and particularly with basic research where the knowledge gained has no obvious or immediate applicability to the pressing problems that confront society. He refers to Sir Eric Ashby's Bernal Lecture pointing out that as recently as ten years ago many people believed that the social benefits of science and technology were largely fortuitous, and that the disorders and shortcomings of society were for the most part beyond the power of man to correct. The landing on the moon changed all that. If this extra-

ordinary achievement of research, technology and organization was possible, then why was it mobilized for so exotic a goal; why should it not be directed toward alleviating the social disorders and problems so critical at home: to issues of the city and the urban poor; to power shortages; to the glaring needs in the field of health care? Why did not the questioners, the people, have a greater voice in the choice of priorities that absorb our energies and resources? Haskins quotes George Bernard Shaw who wrote: "Later on, liberty will not be enough: men will die for human perfection, to which they will sacrifice all their liberty gladly"; and points out that because science is so closely intertwined with both freedom and promise in our culture, the current atmosphere offers both great dangers and great opportunities for its future. He goes on to say "... a nation will be great where it desires greatness, perceives greatness, and rewards and esteems greatness -- and nowhere else. Our general confidence in scientists is a recent development . . . other great episodes of Western culture, such as that of classic Renaissance art, did not persist in fullest creative vigor so very much longer than this. We cannot take endurance and greatness for granted in any facet of our society." We might remind ourselves that no Nobel laureate in science has ever been called to address the Congress of the United States while only a few weeks ago the Home Run King of baseball did so.

What can we do about this state of affairs? As first steps in meeting the problem, Haskins recommends two new kinds of scientific function. One is the public interpretation of science by a group of the best-trained young scientists; he expresses the hope that such activity might become a respected scientific career. The second is that of thinking and operating creatively at the frontiers between science (pure and applied) and social policy. There is no doubt but that these efforts would improve the situation in which we find ourselves, but whether or when they would lead to a solution is another matter. In a sense, people need to know more about the limitations of science; they are all too ready to attribute to it greater capabilities than it has and to withdraw support when it does not provide rapid cures for grievous ills. What is lacking is a reasonable degree of continuing level funding. There are striking parallels between the pursuit of science and other production enterprises. During the honeymoon of biomedical science with the Congress, money was poured into the universities; Ph.D. programs were vastly expanded; the wages paid to professors of biomedical science tripled and quadrupled that of their colleagues in the humanities. Today there are more Ph.D.'s than there are positions available; approved research projects are not being funded; medical schools are threatened with bankruptcy, and the Federal government is called upon to come to the rescue. A year ago the demand for meat was greater than the supply; producer's incomes rose to unprecedented levels; today there are more cattle than can be sold; meat prices have fallen; cattlemen are going into bankruptcy; young chicks are being killed since the cost of bringing them to chickenhood is greater than the price at which they can be sold; the Federal government is being called upon to come to the rescue. This juxtaposition of enterprises may not be flattering to either, but perhaps there are fundamental laws applying to both situations which are being ignored.

The pressures which are being experienced by the biomedical research establishment as a whole have affected the intramural research program as well. The

years of plenty ended abruptly before we brought all our undertakings to optimal strength. We have not yet recovered from the impact of losing almost one-fifth of our permanent positions. Even if we could be assured that our present level of support would continue indefinitely, we face complex management problems in our efforts to distribute resources in the most effective manner. Should we maintain (and possbily strengthen) only those projects and programs which at this moment are the most productive and appear to be breaking new ground? Should we decrease support for investigations in areas which are already reasonably well explored and where the accretion of new knowledge is apt to come more slowly and undramatically? Shall we discontinue altogether our interest in still other areas which, although of great importance for the development of a more powerful behavior theory, are presently showing little or no movement since we must still search for a conceptual breakthrough which might point the way for creative study? In my opinion, these are not simple questions easily answered even in the best of times. And in this period of adversity the answers are more difficult still. There is a natural tendency to increase our efforts only in those areas of research where new knowledge is most rapidly accumulating. A new concept, a new technique, or new instrumentation promise a new understanding of old problems and, perhaps, a means of gaining control over processes hitherto beyond our influence. Research of course is planned but research results cannot as easily be planned for. At an earlier time we were able to maintain a reserve of positions and funds in the program director's office. For reasons beyond our understanding, these could never be officially included in the budget as a managerial device, but were sequestered from unfilled vacancies and unassigned funds. We could immediately give additional support when a research achievement required exploitation or a new idea seemed unusually appealing. Then, over the next year or two, the laboratory would gradually phase out some of its other studies, shift its emphases to the new areas, and we would return the supplemental support to the reserve. Now after a period of personnel freezes, hiring restrictions and cost absorptions, we have no reserve. In some laboratories none of the investigators get the degree of support everyone enjoyed in the early days of the program. With few exceptions we cannot undertake new programs without first discontinuing old undertakings. At the level of the individual scientist, this is not difficult. But at the level of a Section or a Laboratory, it means that a new project or a new program cannot be inaugurated without decreasing or removing some of the resources which had been assigned to other Sections or other Laboratories.

In this period of general retrenchment we have attempted to deal with this problem in several ways. We are seriously considering the disestablishment of some laboratories in the Division and the regrouping of some of the investigators. For example, there are presently studies of child development being carried out in the Laboratory of Socio-environmental Studies, the Laboratory of Psychology and the Child Research Branch. Investigators from all three groups are presently meeting to consider the possible advantages of their coming together in a new Laboratory of Child Development. This would not immediately result in any increase in resources devoted to this critical area of investigation; but plans for future research might take particular advantage of the assortment of strengths available in the new group and increase the power of each investigator thereby. Several staff members are leaving the program for

professorial appointments at Universities; these include Drs. Richard Bell and Robert Ryder of the Child Research Branch; David Reiss and Helm Stierlin of the Adult Psychiatry Branch, and Roger Burton of the Laboratory of Socio-environmental Studies. Dr. Frederick Snyder is leaving the Laboratory of Clinical Psychobiology for an assignment to the Indian Health Service Hospital in Gallup, New Mexico. Dr. Thomas Chase is moving to the National Institute of Neurological Diseases and Stroke as Scientific Director.

For the most part, we do not plan to replace these investigators with other senior scientists of equal distinction, but will instead use their positions and the resources assigned them to reinforce selected existing programs. The Clinical Center setting is particularly favorable for studies of the biological processes which mediate behavior; Dr. William Bunney is shifting the work of the Adult Psychiatry Branch in this direction. Nevertheless, the study of personality development must continue as a central concern on psychiatric research. Despite the difficulties of carrying on such work in a biological institute which seeks repeatedly to replace every interview room with a "wet lab", we consider it essential to maintain a strong interest in this vital area. While we recognize the possibility of increasing our control over some maladaptive behavior as we learn to manipulate neural mechanisms, we believe that mutual understanding between persons and between peoples depends on knowledge of the ways in which experiences determine concepts, values and sentiments and thereby shape behavior. We accept the fact that progress in this area will for a time be much slower than in biology. A wise man said, "Understanding the atom is child's play compared to understanding child's play." The importance of understanding both hardly needs the emphasis afforded by the recent disarmament conference.

ANNUAL REPORT OF THE ADULT PSYCHIATRY BRANCH
National Institute of Mental Health
July 1, 1973 - June 30, 1974

William E. Bunney, Jr., M.D.

The Adult Psychiatry Branch has been in the process of transition since Dr. Lyman Wynne resigned as Chief in 1971. On 14 November 1973, Dr. William Bunney took over as the new Chief of the Branch. The process of change in the Branch has accelerated since November. The general focus is moving from a more psychological focus to a more biological emphasis. This annual report, therefore, reflects that change and includes a number of projects that are being terminated and a number of projects that are in the process of being initiated.

The Branch is currently being reorganized, since new programs are being developed which cannot be included in the former sections and since five of the former sections will be discontinued. Discontinuation of these programs is due to the shift in emphasis and to the fact that a number of Senior Investigators have left or are planning to leave. Five new Sections will be created. In addition to these, two Sections from the previous administrative structure of the Adult Psychiatry Branch will be retained as Units. One is in the Office of the Chief and the other in the Section on Psychogenetics. The Branch will place emphasis on bringing together information from four disciplines to the investigations of depression, schizophrenia, drug abuse and childhood mental illness. These disciplines include pharmacology, genetics, biochemistry and psychiatry. It is proposed that sections be developed around the two clinical psychiatric research wards, 4-East and 3-West, which are administered by the Branch. One of these Sections will be entitled Section on Psychobiology and will focus on depression. The second will be entitled Section on Neuropsychopharmacology and will focus on problems of schizophrenia. In addition, a clinical section will be established on Drug Abuse and will admit patients to two beds on each of the wards 4-East and 3-West.

Two support sections will be developed for the two wards. First is the Section on Psychogenetics, which will facilitate genetic studies. The second support section, entitled Section on Biochemistry, will provide biochemical support for the two clinical wards. Within the Office of the Chief, a Unit on Childhood Mental Illness will be established. This Unit will have a two-fold purpose: a) to study the children of manic-depressive patients who have evidence of genetic factors in their family trees, in order to develop predictors of which children are susceptible to developing the illness; and, b) to study hyperactivity in children.

A maximum effort has been made to support those investigators who are leaving in order to facilitate the analysis and publication of the data which has been collected over the past few years. In most instances, this has involved providing secretarial and research assistant support during the period 1973-1974, and in some instances, this will continue through 1974-1975. It is felt that this approach has tended to decrease the individual stress and trauma of the change in the program and provides for the full exploitation of the previous

research efforts.

To date, Dr. Post has been recruited to work on Ward 3-West in the area of psychobiological studies of depression and Dr. Elliot Gershon has been recruited to work in the area of psychogenetics in manic-depressive patients. It has also been necessary in a very short period of time to recruit almost a full complement of Clinical Associates for 1 July 1974, due to the change in the program's focus. A number of new projects and protocols have been initiated by the Branch Chief during the past year, in collaboration with Dr. Robert Post, and it is anticipated that the next 6-12 months will involve intensive overall research planning and protocol development for the new research efforts in the Branch.

A special attempt is being made to coordinate these new initiatives with the work on the other research wards in the Intramural Program. This is being accomplished through the subcommittees of the newly-established Clinical Investigations Coordinating Committee.

SECTION ON FAMILY STUDIES

Helm Stierlin, M.D.

Along with other changes in the Adult Psychiatry Branch, the Family Studies Section was reorganized and further reduced in scope. It presently consists of Dr. Helm Stierlin, as Acting Chief (working part-time) and a full-time secretary who doubles as a research assistant.

Apart from conducting a few follow-up interviews, Dr. Stierlin, essentially, worked on the material which had accrued during the clinical phase of his longitudinal project, "A Study of the Separation Process in Adolescents and Their Families". This material relates to 43 index patients and their families who passed through this project as either inpatients or outpatients, and to 19 additional families who were seen in screening interviews. Of the 43 families seen in the program, 35 were followed up.

Given the uncertain future of the Section and its relative lack of resources, a decision had to be made as to which lines of inquiry, growing out of the above material, should be given priority. In line with Dr. Stierlin's main interests, three lines of inquiry were pursued by this Section.

First, the conceptualizations on the separation process in adolescence, as outlined in last year's report, were extended, refined and documented with more examples. Here the three transactional modes of binding, delegating, and expelling remained central, yet were now reformulated in order to reflect vicissitudes of one basic delegating process which can derail in two major but opposite ways -- when the adolescent chafes under "missions impossible" that keep him bound-up: or when he is sent out (i.e., pushed into premature autonomy) yet has no meaningful missions to fulfill. This conceptualization was used to further illuminate the phenomenology and dynamics of schizophrenic breakdowns, to distinguish among different types of family dynamics of delinquency, particularly running away, yet also to elucidate the family dynamics in the creative process.

A second major interest was to develop a test instrument that would make the above conceptualizations, particularly the concept of transa[illegible] more researchable and hence, would facilitate a new look at available data. The Section continued to cooperate with Dr. Margaret Singer, focusing on TAT rather than Rorschach protocols, as a potential means for a finer [illegible] tiation between the earlier described family scenarios and separation patterns.

Third, because of urgent treatment demands, particularly for adolescent runaways (presently estimated at 600,000 to 1,000,000 each year in the U.S.) and their families, Dr. Stierlin clarified and formulated treatment principles which grew out of his clinical research practice and concepts.

SECTION ON PSYCHIATRIC ASSESSMENT

William T. Carpenter, M.D.

The work of the Section has again been carried out under difficult circumstances. During most of Fiscal Year 1974, as in Fiscal Year 1973, the Section operated without assurance of future support. In late February, 1974, it was learned that support for this Section would end July 1, 1974, with remaining programs in the Section on Psychiatric Assessment being phased out in the ensuing year.

The primary goals of the Section are: (1) to develop diagnostic concepts and categories that will have more meaningful relationships to etiology, course of illness, and response to treatment than diagnostic systems currently in use; (2) to search for objective validating criteria (with or without etiologic implications) for diagnosis: and (3) to conduct psychobiological investigations in acute, drug-free schizophrenic patients.

The need for improved diagnostic categories has been amply documented by the numerous research efforts in the epidemiology, treatment, psychophysiology and biochemistry of psychiatric disorder that have been hindered by the lack of reliability and validity of the currently used diagnostic categories.

At present, psychiatric diagnostic categories are not validated by objective criteria. Course of illness has not proven as satisfactory as once hoped. The use of relatives' psychiatric histories (genetic loading) and drug response as validating criteria are promising approaches, but still early in their development.

Psychobiological investigations of schizophrenia have rarely been accomplished in severely disturbed, early illness, drug-free patients who have been evaluated with sophisticated clinical research methodology.

International Pilot Study of Schizophrenia: One major activity of the Section has been participation as the U.S. Field Center in the International Pilot Study of Schizophrenia (IPSS) sponsored by the World Health Organization. Other collaborating centers in this project are located in Colombia, Denmark, Czechoslovakia, India, Nigeria, Taiwan, the United Kingdom, and the USSR. The goal of this study is to develop and utilize cross-culturally applicable

interview schedules for the evaluation of psychiatric patients in different countries. These schedules can then serve as a basis for future studies of comparative epidemiology and the cultural and biological factors in psychiatric disorders. Collaborating investigators from the centers have cooperated to develop the interview schedules for eliciting information on current psychiatric status, psychiatric history, social functioning and demographic background and status at time of follow-up examination. To accomplish this, schedules were written, pretested, revised and retested until they were suitable for use in all of the participating countries.

Data has been collected by interviewing 1,202 patients in the participating countries. Two-year and five-year follow-up interviews have been done using forms developed in the IPSS for evaluating course of illness and changes in social functioning. This information provides a basis for comparing the course of illness of patients with different symptoms and different forms of treatment in diverse cultures.

In this study, standard psychiatric assessment techniques have been used for the first time in both initial evaluation and follow-up on a large scale by local investigators in several different parts of the world. Cross-cultural data on similarities and differences of patients from these countries have been obtained. The data analyses on the initial evaluations have been carried out and the Report of the IPSS, Vol. I, was published in 1973. Data analysis of the two-year follow-up has been completed and Vol. II of the IPSS has been drafted. All nine field research centers are presently collecting five-year follow-up data. Data collection is virtually complete in our Center and analysis is underway.

In collaboration with Drs. Gunderson and Strauss, diagnostic criteria have been identified for separating borderline patients from schizophrenic patients. These can be operationalized and, when used, reveal that the two patient groups are comparable in premorbid and outcome features while distinct in their clinical manifestations. Schizophrenic patients had more hallucinations and delusions, while the borderline group had more depersonalization and derealization experiences. Borderline patients are more likely to have psychopathologic anger and less likely to be anxious. The frequency of depression was equal in the two groups, but more severe in the borderline patients. In another study of diagnostic criteria done in collaboration with Drs. Ablon, Strauss and Goodwin, discriminate function analysis techniques were used to develop criteria for differentiating among manic, excited schizo-affective and excited schizophrenic patients. The use of seven symptom criteria successfully separates the manic patients from the remaining two groups, but a second step is required to distinguish schizo-affective from schizophrenic subjects.

Methodology for Analyzing Data for Psychiatric Diagnosis: The Section, together with Dr. John Bartko of the Theoretical Statistics and Mathematics Group, has evaluated and adapted clustering techniques for defining types of psychiatric patients. Such clustering techniques are minimally influenced by theoretical bias, and let the data itself define the "natural groups" that constitute the patient population. The application of cluster techniques to psychiatric data poses many serious problems arising from both the mathematical

properties of the techniques used, and the way in which clustering techniques reinterpret the usual clinical diagnostic modes. In the past year, the investigators have defined more clearly the nature of these problems, and explored modification that will provide more useful applications of cluster analysis to psychiatric diagnosis. Cluster analytic techniques applied to the IPSS patients has revealed interesting patient groupings. They suggest alternative traditional subtypes. Affective psychoses are readily identified by cluster analysis and this approach also supports the diagnostic concept of a schizoaffective schizophrenia category separate from affective disorders.

Comparative Study of Diagnostic Systems: Different diagnostic systems are being evaluated using past psychiatric history and follow-up status as criteria for the validity of diagnostic types. At first, four diagnostic systems were investigated: (1) clinical diagnoses using the APA Diagnostic Manual; (2) computer-derived clinical diagnoses developed by J.K. Wing in London; (3) Lorr's Psychotic Types based on the In-patient Multidimensional Psychiatric Scale; and (4) clusters of psychiatric patients developed from the cluster techniques described in the preceding paragraph. Results indicated that none of the four diagnostic systems was able to predict significantly two-year follow-up status or to postdict earlier psychiatric history. On the other hand, use of multiple regression techniques demonstrates that prognostic items correlate highly with follow-up status. These results replicate results of other studies regarding the relationship of past history to future outcome, but also suggest the lack of utility of several diagnostic systems for the prediction of outcome. These findings suggest that dimensions of function are more important than diagnostic systems and symptomatology in determining outcome in schizophrenia.

To further evaluate other diagnostic systems, the criteria of schizophrenia by Kurt Schneider were used to classify American IPSS patients and NIMH manic-depressive patients. This first empirical test of Schneider's diagnostic system, which is accepted throughout most of the world, refuted his claim for pathognomonic symptoms in schizophrenia. This finding has now been replicated using data from each of the eight other countries participating in the IPSS.

Analysis of variance in the IPSS data has allowed a new group of highly discriminating signs and symptoms to be incorporated into a more flexible diagnostic system which will permit researchers to generate comparable groups for schizophrenia studies and clinicians to diagnose more reliably. Based on 17 clinical inquiries of high reliability, 12 signs and symptoms are rated present or absent. A simple 12-point system was established which can be used in various clinical and research settings to identify schizophrenic patients. This approach includes an estimate of diagnostic error. The system was derived from 550 patients from nine countries and replicated in a second cohort of equal size.

Another diagnostic concept of schizophrenia widely used, especially in Europe, was evaluated in terms of the IPSS data. Langfeldt's concept of schizophrenia has been extensively used, especially in the Scandanavian countries, and many studies have demonstrated its ability to select a poor outcome group of schizophrenics. In an attempt to replicate these findings,

the Washington patients of the IPSS cohort were classified according to Langfeldt's criteria. The two-year outcome of the patients categorized as schizophrenic in this way was compared to the two-year outcome of the rest of the cohort. No significant difference was found in the outcome status of the two groups. This finding challenges the frequently accepted conclusion that the Langfeldt criteria of schizophrenia are adequate to define a disorder with poor outcome, and suggests that failure to control for such factors as duration of illness prior to initial evaluation has been a hidden determinant of outcome in these earlier studies.

Earlier work with Langfeldt's criteria was replicated, using five-year follow-up data from the Washington Center. Also, carefully made diagnoses using a system such as Schneider's first rank symptoms does not select a poor outcome group. The 12-point flexible diagnostic system developed by the Section was used to determine that the certainty of schizophrenic diagnosis does not predict outcome. Furthermore, using two-year outcome data determined that certain non-diagnostic prognostic variables predict future functioning. The best general predictors of two-year outcome are duration of hospitalization in the past, social functioning, and work function.

Standardized clinical instruments have been developed to provide a coordinated system for evaluating patient symptomatology and behavior. These include (1) Psychiatric Assessment Interview, derived from the Present State Examination used in the IPSS; (2) a 34-item daily nursing rating scale; (3) a scale for rating integration and sealing-over; (4) outcome scale; (5) prognostic scale; (6) special features ego scale. Further, scales developed by other investigators have been utilized in the patient population.

Extensive reliability assessment of these scales has been undertaken with satisfactory results. A study which compared data obtained in a structured research interview with data obtained in a detailed clinical work-up over three weeks of hospitalization revealed that comparable symptom information is obtained but that the structured research interview fails to elicit adequate information regarding psychopathologic signs.

A number of biological investigations have been undertaken and can be summarized as follows: (1) leukocyte abnormalities have been used by investigators in Prague to discriminate between normals, neurotics and psychotic patients. Normals, acute schizophrenics, recovered schizophrenics and schizophrenic patients at one-year follow-up all had the same rate of leucocyte nuclear deterioration and this rate was comparable to that found in the psychotic patients by the Prague investigators. Thus, it would appear that our failure to replicate their findings was not based on difference in diagnostic criteria. (2) No evidence was found of systematic abnormality in cortisol metabolism. Investigations in collaboration with other units may shed some light on the relationship between cortisol metabolism, psychophysiologic and clinical variables. (3) Working collaboratively with Dr. Harold Himwich in Galesburg, Illinois, it was not possible to distinguish schizophrenic patients from normals based on a probable transmethylating enzyme in the serum or based on hallucinogenic substances DMT and bufotenin in the urine. (4) In collaboration with Drs. Murphy and Wyatt, it was demonstrated that only mild reduction in platelet MAO activity occurred in our patients. They are

distinctly higher than a cohort of chronic schizophrenic patients. A detailed examination of the relationship of platelet MAO activity to a variety of clinical variables is underway. (5) A number of psychophysiologic investigations have been carried out in our patient group. Data analysis will shortly be undertaken on a group of over 50 patients evaluated in collaboration with Dr. Ted Zahn. Findings from evaluation of average evoked response are reported from the Section on Perceptual and Cognitive Studies (Dr. Buchsbaum). In collaboration with Dr. Williams, it was found that forearm blood flow changes are inconsistent predictors of behavioral changes although some interesting apparent relationships are seen in several patients. More definitive data analysis is currently being done. (6) In collaboration with Drs. Gillin and Henkin, it was found that zinc levels are normal in gastric secretion, fingernails, serum and urine. More patients are being included for evaluation of zinc content presently to determine whether or not a zinc deficiency in hair in our earlier cases can be replicated. (7) Baseline assessment of metabolites of serotonin, dopamine, and norepinephrine in cerebrospinal fluid appear normal and accumulation of serotonin and dopamine metabolites after probenecid appears normal. However, these turnover rates are higher during the sick phase than recovery phase in our patients, despite both being within the normal range. A detailed assessment of clinical features in relationship to these changes is currently being undertaken by Dr. Fink. This work is being done in collaboration with Drs. Post and Goodwin. (8) Screening procedures worked collaboratively with Dr. Torrey and others for 50 viral antibodies have been negative. More detailed evaluation in immunology and virology in schizophrenia is in progress.

Several members of the Section staff are working on a definition of integration and sealing-over as concepts which can be usefully applied to understanding a patient's reaction to his psychotic experience and his style of resolution. A definition of these concepts has been operationalized into a rating schedule that will permit us to place patients into one or the other of these categories. Exploration of their expression through art, their participation in treatment, their outcome and psychobiological indices will be utilized in an attempt to determine whether these styles of recovery are distinguishing features and predictive of other variables.

Several investigators in the Section have examined the interface between clinical and research programs on the Unit and have found that patients fail to make a clear distinction between their participation in therapeutic and research procedures. Information is generated in the context of research procedures which is illuminating to the psychotherapist in his work with the patients. Participation in research procedures also provides illustrative material for a 3-stage concept of resolution of psychoses. The effect of a research atmosphere on an individual patient's treatment has been examined and will be reported. The effect of the ward's organization on a patient's successful participation in research has been the focus of attention with an emphasis on group function rather than individual intrapsychic conflicts as a determinant of successful participation. The failure to complete agreed-upon tasks, when the Unit is dominated by covert goals, has been described and emergency and crisis conditions on a psychiatric unit have been defined.

SECTION ON PERSONALITY DEVELOPMENT

Roger Shapiro, M.D.

The over-all objectives of Drs. Roger Shapiro, John Zinner, David Berkowitz and Edward Shapiro in the Section on Personality Development have been investigation of individual adolescent personality development in the context of his family. They have evolved a typology of families derived from observation of their interaction in conjoint family therapy. In particular, they have characterized families of adolescents with borderline and narcissistic symptomatology, adolescents who do antisocial acting out, and adolescents who are severely neurotic.

Drs. Shapiro and Hauser are completing the longitudinal assessment of cognition and identify formation in early and late adolescence, contrasting the performance of adolescents in the patient sample and non-patient adolescents at Sidwell Friends School.

1. Treatment of Disturbed Adolescents and Their Families

Study of families of borderline adolescents, of antisocial acting-out adolescents, and of neurotic adolescents has continued with observation of conjoint family therapy, of marital therapy of the parents, and of intensive individual therapy of the adolescent. Excerpts of family interaction containing defensive delineations of these adolescents by the parents have been done to characterize the psychodynamic characteristics of the family, and the unconscious assumptions of the family as a group. Data from the individual psychotherapy of the adolescent is the basis of formulations about the state of the ego in the adolescent, his capacity for object relations and the level of defensive organization.

Comparison of families of borderline adolescents, narcissistic adolescents, antisocial acting-out adolescents, and neurotic adolescents reveals clear differences in the psychodynamic mechanisms determining defensive delineations of the adolescent by the parents. Parents of borderline adolescents manifest primitive splitting and projection of badness as the dominant mechanisms underlying defensive delineations of the index adolescent. Parents of narcissistic adolescents relate to their adolescent offspring as narcissistic objects and use them to maintain their own precarious self-esteem.

Parents of antisocial, acting-out adolescents are more differentiated than the parents of borderline and narcissistic adolescents. Projective mechanisms are the basis of defensive delineations, but the projections are less massive and are likely to be differentiated aspects of impulse life like particular forms of sexual behavior with more differentiated superego responses being retained within the parents. Unconscious assumptions are relatively differentiated unconscious fantasies which differ from family to family but contain in them fantasies originating in one or both parents which are projected by the parents onto the adolescent.

Parents of neurotic adolescents employ predominantly repressive defenses rather than projective defenses. In their defensive delineations of the adolescent

they remain oblivious to major areas of behavior in the adolescent which would [illegible] conflictful for the parents. Their behavior toward the adolescent is frequently dominated by repression of conflict at the Oedipal level in themselves, leading to repressive defenses in delineation of the adolescent [illegible] areas of sexuality, competition and competence. Unconscious assumptions of the family as a group may be inferred which have differentiated and elaborated Oedipal themes.

A typology of families of borderline, antisocial acting-out, and neurotic adolescents has been articulated in this work, supporting a conceptualization of emotional disturbance arising from family and group dynamics rather than a conceptualization of disturbance arising in the separate sick individual.

In June, 1974, work with families of borderline, acting-out and neurotic adolescents will be terminated. Several publications of findings in this work have been completed this year and several more are in preparation.

2. Longitudinal Assessment of Cognition and Identity Formation in Early and Late Adolescents

Dr. Stuart Hauser has continued as a consultant to Dr. Roger Shapiro to complete the investigation of cognition and identity formation in early and late adolescents of both sexes who are of patient and nonpatient status. Several contrasts of interest are built into the design; patients-vs.-non-patients; early-vs.-late adolescents; male-vs.-female adolescents; and each of the main groupings (patients and non-patients) can be subdivided in terms of sex and age for intra-group comparisons as well. All of these subjects have been studied over a two-year period.

The instruments for studying the subjects include a self-image interview, a Q-sort, and a battery of cognitive tests. The Q-sort is a major technique of the study as it focuses on self-images. Modifications of the Q-sort Technique developed for this project make it possible to focus more intensively on dimensions of each self-image as well as overall integration and changes in self-images are being analyzed at single points in time, and over spans of time.

The cognitive tests focus on processes of categorization, differentiation, conceptualization and problem solving. The cognitive data is being analyzed in terms of sub-sample differences at single points in time. In addition, correlations and parallels between self-image results and cognitive results are being done.

SECTION ON TWIN AND SIBLING STUDIES

Richard Wyatt, M.D.

The last year has been a difficult one for the Section on Twin and Sibling Studies. Dr. William Pollin, who has been Chief of the Section since its inception, has continued his important and time-consuming roles in the NIMH Task Force, the U.S.-U.S.S.R. Schizophrenia Exchange, and the Drug Abuse Institute. Dr. Richard Wyatt became Acting Chief of the Section in July,

1972, and led a successful effort to continue Dr. Pollin's projects and to begin new ones. An unusually good working relationship between Drs. Pollin and Wyatt and an excellent esprit de corps among the Section's staff created a productive and strong research group. The onset of Dr. Wyatt's serious illness in the summer of 1973 and his resultant absences from the Section for medical treatment have certainly tested the strength of the Section.

A major thrust of the Section's efforts this year was the continued study of platelet monoamine oxidase (MAO) as a genetic marker of schizophrenia. Polyacrilamide gel electrophoresis has been used to look for differences in protein structure between the MAO from schizophrenic patients and that from controls. Numerous technical problems with the electrophoresis have postponed a clear answer so far to the scientific question. But a by-product of the work has been the development of a wet laboratory in one of the Section's office suites, complete with freezer, ultra-cold storage freezer, distilled water, centrifuge, glassware and conveniently arranged laboratory disposables.

In collaboration with Drs. Buchsbaum, Murphy and Goodwin, studies have been done of platelet and plasma MAO in relation to MMPI variables in 100 normal volunteers, platelet MAO in relation to urinary MHPG excretion, and platelet MAO in relation to probenecid accumulation of monoamine metabolites in the CSF. A large study of platelet MAO changes during the menstrual cycle revealed a 23% effect from peak to trough on platelet MAO activity.

A large collaborative study with the National Heart and Lung Institute on behavioral predictors of coronary artery disease among Type II hypercholesteremic patients was successfully concluded after 84 patients were blindly interviewed and tested. Preliminary data analysis suggests that in this group of patients with a large genetic and metabolic risk for coronary artery disease, the Type A behavior pattern does <u>not</u> seem to predict coronary artery disease.

A longitudinal study of ten sets of twins followed since birth by the Section continues under Drs. Martin Allen, a former member of the Section, who continues as a consultant, and Stanley Greenspan. Dr. Allen has also completed this year the analysis of the affective disorders data from the National Academy of Sciences Twin Register. Previous analysis of the schizophrenia and neurosis data from the register have already been published by members of the Section. Dr. Eleanor Dibble and Dr. Donald Cohen, now at the Yale Child Study Center, are using the MZ-DZ intrapair twin comparison method to study heritable factors in the personality development of 425 pairs of twins.

It is hoped that when Dr. Wyatt returns full-time to NIMH between June and September of 1974, that the work will continue with renewed vigor. There will certainly be opportunities for collaboration with the new Section on Psychogenetics in the Adult Psychiatry Branch, to be started under Dr. Elliot Gershon.

SECTION ON EXPERIMENTAL GROUP AND FAMILY STUDIES

David Reiss, M.D.

The primary focus for investigation in this Section has been the mechanisms by which families organize their interrelationships with their surrounding social communities. The major method for investigating these fundamental processes in family life has been precise experimental studies using the small group-type laboratory; more recently, the Section has developed questionnaire and survey techniques. This year the Section pursued work along three closely related lines. First were studies aimed at developing conceptual and methodological tools for directly and objectively measuring salient characteristics of the family's social environment. Second were studies of the interaction patterns of families with that environment. Third were detailed studies of the mechanisms families use in the preliminary, adjustment stages of adaptation to a new environment.

Assessing the Social Environment. In this work, the Section has sought to conceptualize and measure those aspects of the social environment most likely to influence or control the interaction of families living within it. As an initial site for observations, the Section chose the psychiatric hospital and the families of patients admitted to one of its wards. Data analysis, completed this year, showed strong evidence that the values and objectives of the hospital, as experienced by its staff, have strong influence on small group interaction within the hospital social organization: it is likely, though no direct evidence is yet available from our studies, that these same values and objectives would have a profound impact on family groups. Data analyzed this year have revealed that a great diversity of values and objectives, in the hospital, can be exhaustively characterized by the use of three conceptually and statistically distinct dimensions: the importance, in this hospital, of fostering close and warm personal relationships among staff and between staff and patients: the importance, in this hospital, of depending on conventional and established lines of authority: and the importance, in this hospital, of sharing responsibility for patient improvement. These three values appear to underly the major objectives, norms and interaction styles in psychiatric hospitals.

The Family's Interaction with its Environment. Previous investigation in the Section's laboratory suggests that a family's adaptation to a new social community is a two-stage process. First, the family's collective response is determined by a stable, collective disposition we have called typical consensual experience: this determines whether the family will actively explore its new surroundings or retreat from it and, also, if it explores its new surroundings, how it will interpret the data. Second, as a result of explorations, conditioned by its basic collective disposition, the family forms a shared construct of its immediate social environment. This shared construct determines its collective interaction with other families and staff. The Section's investigators suspect that ward values may alter this construct in some families indirectly by determining the form of its preliminary investigations but this aspect was not directly studied in the present investigation. If the theory is correct one should be able to predict specific family constructs from knowledge of its basic, collective dispositions. The latter

can be measured by the oft-used laboratory procedures, particularly the family pattern recognition task. For the former, the investigators developed two new procedures: the family perception test (which tests a family's construct of other families on the ward) and a ward perception Q sort which tests the family's construct of the ward as a unitary social community. A second test of the theory is to use the family construct data to predict the pattern of interaction between the family and ward. The latter is measured by objective verbal and non-verbal indices also developed specifically for this study. Although data collection on this project is not yet complete, preliminary analyses show that the families very quickly develop stable and measurable patterns of interaction with the ward community which are predictable from their performance in the laboratory. For example, families who, in the laboratory, pay a great deal of attention to one another's ideas and behaviors, appear to interact more with one another and less with non-family members in the ward situation.

Mechanisms of Early Adjustment of the Family to its Social Community. Evidence collected in the Section's laboratory and elsewhere suggests that family members give each other subtle cues about their immediate reactions to a novel social situation; these cues are quickly elaborated by the family into a shared or united response, as a group, to the new social situation. During the year, the Section completed data collection and most data analyses on an experiment to study these covert, non-verbal cues. Preliminary data analysis confirms the hypothesis concerning the importance of this cue system but further analysis is required to explore the specific differences in cues predicted for families with different patterns of adjustment.

SECTION ON PERCEPTUAL AND COGNITIVE STUDIES

Monte Buchsbaum, M.D.

The goal of the Section is to relate individual differences in sensory perception and cognitive functioning in human subjects to the underlying neurobiology of psychiatric illness. From these studies it is hoped to develop and implement clinically valuable measures of neurophysiologic function. The finding of perceptual and attentional deficits in a variety of psychiatric patient groups has encouraged the development of theories of psychiatric illness based on perceptual style. However, the psychiatric patient's report of his perceptions might reflect poor motivation, poor cooperation, failure to attend to instructions or inability to communicate with his examiner, rather than any perjeptual difference. For this reason, the Section has emphasized electrophysiological correlates of perceptual behavior using average evoked response (AER) techniques which demand relatively little active participation from the subject.

It has been reported previously that bipolar affective disorder patients show relatively greater rates of increase of visual AER amplitude with increasing stimulus intensity (augmenting) in comparison with unipolar or schizophrenic patients who often show actual decreases in amplitude (reducing).

Based on a series of studies in both normal subjects and patients, AER [illegible] appears to be associated with a tendency to seek excitement and to be insensitive to weak stimuli. Reducing, in contrast, is linked to avoiding excitement, sensitivity to weak stimuli and pain tolerance.

Recently, correlations between AER scores and individual differences in both pharmacologic response to psychoactive drugs and platelet MAO levels have led to intense investigation of these relationships.

The AER amplitude/intensity slope is negatively correlated with platelet MAO in normal, schizophrenic and unipolar patients. Since both schizophrenics and bipolar patients have low MAO levels and are relatively well differentiated by the AER whereas unipolar and schizophrenics are reducers but well differentiated by MAO, multivariate analysis was applied. A large group of bipolar, unipolar and schizophrenic patients and 49 normal controls with approximately the same age distribution were used: males and females were analyzed separately. In both sexes, combined classification of the four categories was quite successful with over 72% of the subjects classified correctly; most prominent misclassification errors were normals classed as schizophrenics.

These misclassification errors suggested the possibility of "schizophrenia spectrum disorders" in the normal group -- estimated by David Rosenthal to occur at about this incidence. Individuals with both AER reducing and low MAO might be postulated to be at increased high risk for development of schizophrenia, affective illness, or subclinical symptoms of either. A major study has been started to locate normal individuals with extreme values of MAO and to study them and their families with AER, personality scales and other biochemical measures.

The AER is also being used as a predictor of individual response to amphetamine. Among off-medication hyperactive children, we have noted that augmenters with some AER signs of developmental lag respond favorably clinically to amphetamine: AER's change in the reducing direction (toward normal). In contrast, children with reducing and mature AER patterns tend to augment on amphetamine and deteriorate clinically. This finding has led to studies of d- and l-amphetamine in patients with affective disorders. Preliminary results in 11 patients indicate significantly greater effects with l-amphetamine than with d-amphetamine.

Individual differences in serum DBH, while so far uncorrelated with the augmenting/reducing dimension, appear related to individual differences in focusing attention. AER amplitude usually increases when subjects are asked to make perceptual judgments about the stimuli instead of merely sitting passively. In several different experimental paradigms, the magnitude of this increase has been highly correlated with DBH. In one study, the mean DBH of all individuals who showed an AER amplitude attentional increase was 10.0: and of those who showed an AER fall with attention was 3.0. This finding is being pursued with more detailed attentional studies in both normals and patients. Intriguing possibilities are suggested by the finding that schizophrenics, long postulated to have an attentional deficit, have also been implicated as having low CNS DBH (although the relation between

central and peripheral DBH is quite uncertain).

Taken together, these studies indicate that AER techniques might yield useful indicators of the functional status of various neurotransmitter systems. Remarkable individual differences found in the assayed levels of the various enzymes, the wide overlap between patient and normal subject samples with all biological measures and the increased diagnostic efficiency of combining biochemical and neurophysiological techniques suggest the fruitfulness of a collaborative approach to these issues in psychobiology.

3-WEST CLINICAL RESEARCH UNIT

Robert M. Post, M.D.

In the first year of its development, the 3-West Clinical Research Unit has focused investigation on the psychobiology of acute psychoses, manic-depressive illness and schizophrenia. Methodology revolves around longitudinal assessment of patients during drug-free and treatment periods before and after clinical remission. Patients are rated twice daily on a double-blind basis by nursing staff on global and more detailed psychopathology scales. This running quantitative clinical description of the patient then forms the framework for evaluation of new drugs and therapies and correlation with other biological and behavioral data. For example, a telemetric system for accurately measuring patients' motor activity has been developed, providing ongoing documentation of different activity levels in various illnesses (such as agitated vs. retarded depression) and in response to therapy.

Evaluation of central amine metabolism as reflected in cerebrospinal fluid and urinary metabolites is a major tool in this longitudinal assessment. The effects of antidepressant treatments (such as lithium, tricyclics and electroconvulsive therapy) and neuroleptics (such as thorazine, thioridazine and pimozide) are then determined. Systematic effects of the major antidepressant treatments on serotonin turnover have been documented, while the neuroleptics predominantly affect dopamine turnover. Methodological problems involved in the study of amine metabolism are being explored in non-human primates and new techniques, such as mass fragmentography, are being utilized in collaboration with the Laboratory of Clinical Science for confirmation of assays by fluorometric and gas chromatographic techniques. Intense focus is also being given to problems of interpretation of biological-behavioral data, especially in separating primary or etiological biological changes from those that are secondary or epiphenomena of the psychiatric illness. For example, major changes in amine metabolism in relation to activity and stress have been demonstrated. Evidence is also accumulating that decreases in the norepinephrine metabolite, MHPG, in CSF during depression may reflect a state-independent biological change which does not normalize with recovery, but may represent an underlying predisposition to depression. Similarly, the serotonin metabolite, 5HIAA, which appears to be decreased in some depressed patients, is paradoxically reduced further during treatment. Illustrative of attempts to study biological-behavioral interactions is the intense study of a patient with regular cycles between mania and depression in whom daily measures of EEG-monitored sleep, activity, mood, evoked potentials, amine metabolites and amines and enzymes in platelets and

plasma are studied. Rapid switches in mood have been related to dynamically significant events as well as to slow changes in [illegible] parameters which may modulate and reach critical thresholds for acute changes. Biological alterations prior to, coincident with, and following mood switches have been documented.

New focus has been given to the area of the neuronal receptor site in psychotic illness and its modulating effects on presynaptic function. Agents such as clonidine and ET 495, which affect norepinephrine and dopamine receptors rather specifically, are being investigated in acutely ill patients. Changes in CSF (as well as plasma) electrolytes during ECT have been documented for the first time and changes in calcium levels with lithium treatment appear to predict clinical response. Thus, a major focus is not only documenting underlying biological changes during illness but also classifying patients and predicting which treatments may be clinically effective.

Parallel work has proceeded in developing a primate facility for the clarification and development of new techniques for use in man and for study of models of psychosis. Studies of the origin of amine metabolites in CSF and their response to probenecid are being conducted. Following the observations that administration of stimulants such as cocaine in man may result in manic-like euphoria, depressive-like dysphoria and schizophreniform paranoid psychoses, cocaine is being administered to monkeys to assess biochemical-behavioral effects. Marked changes in activity, attention, posture, and stereotyped behavior have been observed and are being correlated with changes in norepinephrine and turnover of dopamine and serotonin during acute and chronic cocaine administration. The effects of neurotransmitter precursors and blockers on behavior patterns in rats, especially motor activity, have also been studied as model systems for assessment of behavioral-biochemical relationships.

1974

Annual Report of the Child Research Branch

Division of Clinical and Behavioral Research

National Institute of Mental Health

Richard Q. Bell, Ph.D., Chief

The Child Research Branch was organized to carry out longitudinal studies in which the separate contributions of preparental and congenital characteristics are identified during the early phase of the life cycle (newlywed period to the preschool period for the first born), in order to throw light on the origins of social, emotional, and cognitive development. Starting in 1966, four separate teams of investigators, each specialized in one particular phase of development, and collecting their data without prior knowledge of information from the other assessments, studied several hundred newlyweds, and over 100 of their offspring. All data collection has been completed, and the various teams are in different stages of analysis.

Although all of the teams are now currently engaged in work on the main cohort of the longitudinal study, some work from the period prior to 1966 appears in the project reports, including short-term longitudinal or cross-sectional studies. To help the reader keep track of these separate efforts, the term "preparatory studies" is used to refer to projects carried out prior to the launching of the main longitudinal study in 1966. Other terms include "within-stage" (data gathering or analysis within a phase of development for which a given team is responsible) and "cross-stage" analyses (longitudinal relations between the periods of early marriage, pregnancy, the newborn period, the third month postpartum, eleventh month postpartum, and the early preschool period). "Cross-method" and "cross-setting" analyses involve efforts to locate variables or sets of variables that have applicability beyond a specific questionnaire, interview, interaction procedure or other situation in which information is gathered. "Dimensional" or "factorial" studies refer to efforts to locate general variables underlying a large number of measures. Individual composite or summary scores are computed to represent these factors.

Throughout the reports of the various research teams it will be seen that there is a common preoccupation with the precision and power of the measures used to characterize subjects in a given stage. While such objectives are important in all scientific research, in experimental studies the simple expansion of the sample, or manipulation of an independent variable, can make it possible to demonstrate effects despite substantial variable error. By contrast, when following up the same cases over a long time period, variable error due to uncontrolled events that occur between stages in the life history of the cases is added to the usual variable

error encountered in all behavioral science assessment. Special efforts must be made to eliminate errors of measurement, reduce discrepancies between different observations of the same event, eliminate the contribution of temporary or transient contributors, and build up the summarizing power of measures, in order to keep the many vicissitudes in human lives from obscuring important traces of early event sequences.

For the above reasons, some bodies of data have been recomputed several times to eliminate or reduce errors to the bare minimum. Measures that have met very stringent criteria relative to observational accuracy are checked further to see whether they characterize the cases over a short time period, since even very reliably recorded information may be specific to a given hour or day in the life of a subject, and have little meaning beyond a given assessment. Studies of short-term stability have been repeated with different approaches in order to be sure that measures actually reflect stable individual differences. In addition, variables are correlated with known reference measures to ascertain whether expected contextual validity exists. Finally, interrelated measures within a given phase of development are gathered together in a composite or summary score so as to take advantage of the fact that such a composite minimizes the contribution of specific variance, and maximizes the common variance, for whatever value the latter may have in cross-stage analyses. Preparatory work in our project has provided abundant illustrations of the necessities of all of these safeguards, even though they prolong the period of data analysis. The reader will see all stages of our efforts to deal with these problems in the separate project reports, because each team is at a different point in data reduction.

Office of the Chief

With the completion of all data gathering, sufficient staff time has become available to make possible an intensive effort to formulate hypotheses to be tested on data from the main longitudinal study. It has been possible to maintain a series of weekly meetings in which each section reviews all findings from the preparatory studies, as well as from the research literature on marriage and child development as a whole. Since there have been many important empirical and theoretical developments in these fields since our preparatory studies were completed in 1966, it has been necessary to reexamine earlier findings in order to determine whether the interpretations that we have made in the past are still correct. We have reanalyzed data from some of the preparatory projects to guide the process of hypothesis development.

Some exciting new possibilities are available for further testing. It appears that we have sufficient grounds to formulate specific hypotheses that involve the prediction of maternal attending and handling at the third month postpartum from the nature of the early marriage, from the mother's report of her own relations with her parents, and from congenital data available from newborn assessments. There are reasonable bases for expecting that these and other related maternal behaviors will be associated in the new project with social responsiveness of the infant, and later behavior

of the child in the preschool period. Within the next few months we will turn to specific testing of these hypotheses using composite scores or specially selected individual measures that will have been developed and thoroughly evaluated at each phase of development by the time we are ready for the testing. Our current plan is for a given team to undertake the testing of hypotheses involving segments of development for which their own expertise is most appropriate. The results of this series of hypothesis tests will be made available in separate reports to various journals, because of the variety of special interest groups to which the findings will be of significance. The series of reports will then be brought together in a summary volume to be prepared by the Office of the Chief.

A second line of work is being planned to appear in the form of a single volume or monograph, with each of the major investigators contributing separate chapters. This will be a document reporting the samples, procedures and methods, at each phase of development, and the cross-stage relations between composite scores developed to represent the most salient features of each period. Work directed toward the production of this volume is already proceeding in the form of efforts by all sections to carry out factor analyses of their data, following which we will begin the task of interrelating the summary scores representing these factors. It is expected that some of the more complex statistical procedures, such as canonical correlation, multiple regression, and discriminate function, will also be used in relating these composite scores between periods, because the "boiling down" process at each phase will yield a small enough number of composite scores relative to our sample size to make these procedures applicable. Work on the document involving the summary measures is not contingent upon progress made in the other line of activity, namely the testing of specific hypotheses involving specific measures, or theoretically selected sets of measures. Thus our work on the two general aspects of analysis can proceed simultaneously, consistent with the availability of staff time to cover both lines of work. Thus, in summary, our current efforts are directed to one line of endeavor that is primarily theoretical and has as its outcome the testing of specific hypotheses on the main cohort, while the other line of effort is empirical, and consists, in essence, of deriving the most salient and powerful measures to represent development at each phase, and then relating these summary indices to determine what metamorphic and isomorphic continuities exist.

Other scientific activities in the Office of the Chief have consisted of presenting a report at Denver to a conference on research in infancy. This paper reported indications of a congenital contributor to positive emotional expression in our own longitudinal studies from the preparatory period, and from two other longitudinal projects. Following this meeting, I attended the Winter Conference on Brain Research, at which I participated in a series of meetings with investigators carrying out studies of infants at high risk for the development of schizophrenia. We exchanged information on findings and methods common to our longitudinal projects.

This year saw a considerable heightening of interest on the part of university research centers in both our theories of how infants and young

children affect parents, as well as in findings that have emerged up to the present from the preparatory work of the longitudinal project. Throughout the year, I made at least one report, and sometimes two per month, to various university colloquia, or other research groups, on these topics. It is gratifying to see the surge of interest in our work reach this level, just at the time when we are on the threshold of bringing forth the findings from the main cohort.

Section on Family Development

Although there have been many studies of marriage, relatively few have samples from a general population, instead of from clinical sources and university students. Still fewer studies have started in the newlywed period, with data gathered by three methods on substantial samples, and with follow-ups of the same couples. For these reasons, the work of this section will undoubtedly provide the base for many studies of marriage in the next decade, even though it will have served its purpose in the present context. This purpose was to launch a cohort of marriages to be followed for several years in a study of child development. Since this purpose has been served, the section is scheduled for inactivation this fall.

The section has been hampered this last year by our inability to locate a computer programmer to assist in the final analyses, but at the present time has essentially completed the task of creating a bank of manageable and accurate files, to which there can be ready access for a variety of analyses. The raw data from interviews, questionnaires, and interaction situations has been brought through to a stage from which it should soon be possible to derive cross-method factors. The latter will then be incorporated into our analysis of relations between salient measures representing the different phases of the life cycle.

Section on Parent-Infant Behavior

The measurements provided by this section are the key to most longitudinal analyses, either those projecting forward from early marriage and the newborn period, or those going beyond to the early preschool period. Accordingly, from the standpoint of coordinating the pace of work in the various sections, it is very reassuring that the data from pregnancy, and the third postnatal month (both from home observations and laboratory studies) have been brought to a point at which dimensional analyses are under way. Factors have already been developed from attitudes toward the maternal role elicited in pregnancy interviews. Scores representing these factors have shown their meaningfulness by correlating appropriately with the corresponding, but actual, maternal behaviors directly observed in the home at the third postnatal month. These relations only appeared for our upper socio-economic status (SES) families, providing us with a very valuable caution: we might overlook latent patterns if we do not separately identify the effects of SES on our longitudinal relations.

Up to the last year, we envisioned only two ways of isolating the separate contribution of parent and child to the process of early development. One involved relating preparental characteristics to later child outcome, and the other, relating congenital characteristics, mainly from the newborn period, to the same outcome measures. This year, this section has reported further comparisons of maternal behavior with second-born infants and their first-born siblings, using three month home observation variables, that provide one other way of isolating influences. By way of background for the recent findings, it should be mentioned that siblings in the same family usually differ considerably on most characteristics outside of the range of intelligence and physical growth. Accordingly, maternal behaviors that are shown consistently across sibs at this early point in development provide a very interesting estimate of what the mother is contributing to the interaction system. Conversely, measures of her behavior that do not show consistency across sibs are susceptible to the interpretation that they have been influenced by the infant. Accordingly, it was very interesting to find that the mother's physical affection, the distance she maintains from the infant, and her tendency to imitate vocalizations, were consistent across siblings. Controls for age of mother and sibling pattern were available so it was possible to rule out the mother's age as a determining factor, and separately identify the effects of sex of sibling order. To my knowledge, the foregoing finding is the first of its kind, and it is noteworthy that it has an important bearing on various theories of sibling order that have lacked empirical data from early infancy, up to the present time.

One other report from this research team is important in a very basic way. Students of learning theory have assumed that they could extrapolate from the effectiveness of operant conditioning techniques with infants to explanations of the origin of infant behaviors. One of the few studies to actually check on this assumption has been reported this year, and the findings are reassuring in one sense, that relations could be found between home observation measures of vocalization, and variables obtained from a laboratory conditioning procedure. Unfortunately, as far as simple extrapolations between the two sources of data are concerned, the relations differed for the sexes.

Section on Infant Development

In 1971, Dr. Raymond Yang assumed responsibility for a massive set of physiological and behavioral data, collected by a previous team director. Dr. Yang has brought to the task great energy and ingenuity in freeing the data from errors, and from limitations imposed by equipment malfunctions during the period of data collection. He has ably handled many difficult problems involved in deriving dependable behavioral data from observations provided by three different nurses over a three year period.

Dr. Yang has also brought to the work of this section a new theoretical orientation to guide studies of relations to prior and subsequent data. Viewing physiological functioning and the behavioral repertoire of the newborn as not only the beginning point in a social interaction system, but as the end point of a marriage, pregnancy, and fetal exchange process, has

led to a very interesting finding with considerable implications for obstetrical practice (as well as for control over sources of variation in studies of the perinatal situation from which newborn behavior emerges). Viewing newborn behavior as an end point, Dr. Yang and his staff traced the process back to pregnancy, and uncovered a relationship between anxiety measured from a questionnaire completed by the mother in the last trimester of pregnancy, and the amount of sedation given the mother at labor. It has been conjectured by some obstetricians that the response of the anesthetist to extremely anxious mothers is to sedate them heavily during labor, but practices differ greatly amongst physicians, and it is noteworthy that this finding of a positive relationship between anxiety and amount of sedation emerged from a sample serviced by a wide variety of physicians. Dr. Yang has been unable to fill in the next link, between sedatives given the mother and behavior variation in the newborn, but may find relations to behavior in later infancy, as some other investigators have reported.

This section is attempting to develop composite scores based on theoretical considerations, and based on previous follow-up studies from the newborn period, rather than rely entirely on factor analyses to extract dimensions to represent the period. The reason this approach differs from that of other research teams is that follow-ups from the newborn period, carried out in the course of our preparatory studies, indicated that the organization of newborn behavior was to a considerable extent temporary in nature. Thus, the common variance in several measures, that would ordinarily serve as a basis for their being located on the same factor, may have little meaning beyond the newborn period. By way of contrast, if any measure in a preschool factor showed a significant relationship to a prior newborn measure, the other measures with which it shared common variance tended to show a similar cross-stage correlation. Accordingly, it may be necessary to depend on single newborn measures, or composites developed for measures that in previous studies showed similar longitudinal relations, even though the measures do not show strong common factor variance at the newborn period.

The problem of the temporary nature of the organization of newborn behavior makes it especially important that the single measures be stable indices of individual differences. Dr. Yang's staff has gone to special efforts to assess the stability of these individual measures, with various adjustments to compensate for the peculiarities of the newborn repertoire.

Section on Child Behavior

The incredible task of locating over 100 children, arranging for them to come to Washington for a half-day study, or transporting them from all points around the beltway, in case they were still residing within driving range, has been completed by this section this year. Case loss to the preschool study is minimal. The children were transported daily over large distances without major injury, and one of the most comprehensive assessments ever carried out on preschool-age children was completed with minimal omissions for each child. Extensive notes are available on the qualitative

aspects of each child's play, and relations to parents and our staff. Mechanical activity recorders provided quantitative indices of the child's action in different settings. Observations of play behavior have been so frequent as to provide highly stable measures in most categories. Individual testing for language and cognitive development was carried out. All in all, if there are contributors to later development from early marriage and infancy, they should not escape the network of measurement that has been cast by this section.

The stages of data preparation through which other sections have passed are being recapitulated in the preschool analyses. These are moving at a rapid pace because, at the outset of the program, as much of the data as possible was processed weekly in computer form. Studies of observer agreement have been completed, and analyses are moving on to stability of observed behavior. Factor analyses have already been undertaken on data for which test-retest assessments are not feasible (teacher's rating), and several very interesting dimensions have emerged. Observational variables pose difficult problems in psychometrics because of their skewed distributions, but it is expected that these problems will soon be resolved, and it will be possible to carry out factor analyses on the observation measures as well. Following this, cross-method and cross-setting factors will be derived.

In one other line of activity this last year, it was found that continuities can be identified between child behavior in the half-day visit, and that in the full one month of nursery school. These continuities occur in the case of assertive, high intensity behaviors for males, peer behavior for females, and speech development for both sexes. This is an important methodological finding, since the half-day studies provide the maximum follow-up sample, and the division of our cases by sex will leave us in need of all possible cases when we come to cross-stage analyses.

A study reported at a convention this year grew out of further efforts to understand the meaning of what the child does in the half-day visits, but goes beyond our interests in the utility of the visits for the longitudinal study per se. Gale Inoff and Charles Halverson have identified a "disruption of activity" factor that may be separated from other elements occurring during our experimentally arranged encounters of the child with unfamiliar adults during the half-day visit. Since stranger encounters are receiving considerable attention currently in the field of child development, it was helpful to draw attention of other investigators to this aspect, and its differential meaning for young males and females.

Although this section's activities have been concentrated for some time on its contribution to the longitudinal study of the main cohort, a finding from a preparatory study is in press this year. In this latter study one sample of preschoolers was followed up to the early school-age period in order to provide a check on our assumption that pre-school barrier behavior has important long-term meaning. The assumption, on which so much of our longitudinal plans are predicated, was amply supported in the finding that coping behaviors showed stability over a five-year period, and interesting ties to later verbal intelligence, imagination, imitation, and ease in social situations.

Annual Report of the Laboratory of Clinical Science
National Institute of Mental Health
Irwin J. Kopin, M.D., Chief
July 1, 1973 through June 30, 1974

Introduction

The Laboratory of Clinical Science has been altered in administrative structure during this year to reflect more accurately the division of the research program by the various senior investigators. The Section on Psychiatry has been divided into a new Section on Psychiatry, with Dr. Frederick Goodwin as Chief, and a Section on Clinical Psychopharmacology, with Dr. Dennis Murphy as Chief. The former Unit on Histopharmacology was elevated to the status of a Section with Dr. David Jacobowitz as Chief. In addition to these three new sections, there are Sections on Experimental Therapeutics, Pharmacology and Medicine and the Office of the Chief (which includes Units on Clinical Biochemistry, Analytical Biochemistry and Clinical Pharmacology).

The programs of research conducted in the various sections and units of the Laboratory of Clinical Science are directed toward understanding the biological basis of psychiatric and neurologic disorders and how associated abnormalities in the fundamental processes involved in support of neuronal function and integration may be corrected by pharmacological or other interventions. The basic research efforts are aimed toward elucidating the biochemical, neurophysiologic and hormonal processes which affect neuronal growth, development and function and determining how genetic factors, hormones, drugs and environmental stimuli influence these processes. Clinical investigations are directed toward describing pertinent biological abnormalities and providing new information about the metabolism, distribution, and biological effects of various drugs and determining their influence on the course of psychiatric or neurologic disorders. The clinical studies are designed to take advantage of the newest basic biological discoveries and often stimulate new lines of fundamental investigation.

Section on Pharmacology
Julius Axelrod, Ph.D., Chief

The Section on Pharmacology has continued to pursue investigation of the biogenic amines and the mechanisms of control formation, utilization, and actions of these substances.

Drs. Romero and Brownstein observed a circadian rhythm in the norepinephrine turnover in the sympathetic nerves innervating the pineal. This rhythm appears to drive the rhythmic alterations in indoleamine metabolism in the pineal gland. They also found a daily rhythm in the responsiveness of the pineal-β-adrenergic receptor which was found to become most sensitive during the daytime, when release of noradrenaline is most reduced.

Utilizing a variety of methyltransferase enzymes, methods have been developed for measuring picogram amounts of biogenic amines in individual nuclei of rat brain. In collaboration with Dr. Palkovits, Drs. Saavedra and Brownstein have mapped the distribution of serotonin, noradrenaline, dopamine, histamine and tyrosine hydroxylase in about 130 separate nuclei. In collaboration with Dr. Carpenter, Drs. Saavedra and Brownstein have found octopamine-containing neurons in aplysia. They also observed that several putative neurotransmitters can co-exist in single identifiable nerve cell bodies of the aplysia ganglion.

Dr. Ciaranello has found that in the adrenal medulla of a mutant strain of mice, the catecholamine biosynthetic enzymes, tyrosine hydroxylase, dopamine-β-hydroxylase and phenylethanolamine N-methyltransferase appear to be controlled in a common regulatory gene. He also found that fighting behavior in mutant strains of mice is genetically-linked.

Using antibodies to dopamine-β-hydroxylase, Drs. Wooten and Ciaranello demonstrated that hypophysectomy increases the rate of degradation of this enzyme. With Dr. Jacobowitz, they have been able to localize the enzyme in extraneural sites in the salivary gland using an immunofluorescent technique.

Dr. Holz has found that the ionophores X 537A and A 23187 release dopamine from synaptosomes of the corpus striatum by different mechanisms; A 23187 releases by a Ca++ dependent exocytosis, while X 537A releases dopamine into the cytoplasm from an intrasynaptosomal storage vesicle.

Drs. Diliberto and Axelrod have found that the methanol-forming enzyme in the pituitary methylates the carboxyl groups of anterior pituitary peptide hormones. The protein carboxymethyl transferase enzyme has also been found in relatively high concentrations in the rat brain.

Section on Medicine
Irwin J. Kopin, M.D., Chief

Investigations in the Section on Medicine continue to focus on examination of the mechanisms for control of biogenic amine synthesis and the levels of biosynthetic enzymes in various neuronal tissues. Attempts are made to relate drug effects, environmental and genetic factors, endocrine states, and abnormalities in function of brain or peripheral adrenergic neurones to the fundamental processes governing synthesis, storage, release, action and termination of the activity of neurotransmitters.

During the last year a good deal of attention has been directed towards elucidating the mechanisms for amine release and to development of techniques to assess the rate of release of neurotransmitters in experimental states and in Man. Drs. Thoa and Wooten have compared release of dopamine-ß-hydroxylase (DBH) and norepinephrine (NE) from the guinea pig vas deferens stimulated by a variety of drugs or depolarization procedures (high K+) and have been able to show that sympathomimetic amines release norepinephrine from the soluble, unbound stores of the catecholamines by a calcium-independent mechanism, while agents such as veratridine release both DBH and NE from vesicles by a calcium-dependent exocytotic mechanism. The role of other ions and affects of other drugs have also been examined. Dr. Jonathan Moss, with Dr. Thoa, showed that scorpion venom elicits release of NE and DBH from this preparation and certain antibiotics which act as iontophores (ion transporting substances) produce Ca++ dependent exocytosis release (A 23187) while another such substance (X 537A) produces intracellular release which is independent of Ca++. These observations agree with those of Dr. Holz.

The appearance of DBH in the serum has led many investigators to use this enzyme as an index of sympathetic nerve activity, but Drs. Reid and Kopin have shown that the amount of sympathetic neuronal activity has only a transient effect on levels of DBH. Drugs, such as hexamethonium or bretylium, which block ganglionic transmission or neuronal release and markedly depress circulating levels of NE do not decrease DBH levels and other drugs, such as phenoxybenzamine, which enhance NE release do not elevate levels of the enzyme. Control of circulating DBH appears to be related to control of its synthesis rate in the cell body, its subsequent axonal transport and release from the nerve ending by both exocytotic and nonexocytotic mechanisms. Studies of serum levels of DBH in experimental hypertension in rats have been continued and expanded to include examination of circulating catecholamines.

Drs. Thomas and Ziegler have been primarily concerned with DBH in the human serum. They have isolated a protein from human serum which contains DBH activity and have produced an antibody which inactivates the enzyme. There is cross-reactivity of the protein with antibodies to DBH obtained from other laboratories. The levels of immunoreactive DBH appear to be much greater than the serum levels of enzymatically active enzyme, suggesting that once released DBH is converted to an inactive form which retains its antigenicity. This could explain discrepancies between various laboratories in studies relating DBH activity to NE release. In the rat, intravenously administered bovine DBH is rapidly inactivated, but it is not yet clear as to whether or not immunogenicity is retained.

The development of sensitive radiometric methods for estimation of epinephrine and norepinephrine in plasma has resulted in the observation that venous blood from the tail of a rat kept in a warmed environment (34°C) contains only about 15% as much catecholamines as blood obtained from an artery. Removal of the catecholamine during passage through the capillaries of the tail appears to be reduced partially by cocaine, which inhibits neuronal uptake of the amine, but part of the loss is the result of metabolism. These studies by Dr. Roizen were initiated during investigations of the effect of anesthetics on circulating catecholamines. All anesthetics appear to strikingly reduce both epinephrine and norepinephrine in plasma, perhaps in relation to depth of anesthesia. There appears to be a relationship between depth and length of anesthesia to development of supersensitivity to catecholamines which may, in turn, facilitate development of arrhythmias.

Drs. Kizer, Zivin and Brownstein have examined levels of tyrosine hydroxylase in small areas of the hypothalamus after a variety of endocrine manipulations. They have found increases in this enzyme selected nuclei, suggesting that dopamine or norepinephrine synthesis is accelerated in these parts of the brain, which play a role in controlling endocrine responses to alterations in thyroid activity. Similar observations have been made during stresses by Drs. Kobayashi and Palkovits.

Drs. Kobayashi, Palkovits, Jacobowitz and Kopin have examined the effects of lesions of one locus coeruleus (the source of many norepinephrine-containing neurones) and of reserpine on catecholamine content determined biochemically and by histofluorescence. The observations show that the histofluorescence technique is of limited reliability in studying changes in levels of catecholamines and that the locus coeruleus noradrenergic neurones vary in

the extent to which they innervate various parts of the brain and the extent to which there is ipsilateral, bilateral or contralateral innervation.

Dr. Hanbauer has examined the mechanisms involved in elevation of tyrosine hydroxylase in the adrenal medulla and superior cervical ganglia of rats and demonstrated that a β-adrenergic receptor and cyclic AMP appear to be involved in the initial stimulus leading to indication of the enzyme. She has also found that vinblastine, which acts on neurotubules, slows release of NE from the heart and later results in destruction of the sympathetic nerve endings.

Dr. Webb has studied the biochemical changes in explanted sympathetic ganglia. There is a marked elevation of NE and DBH, particularly in the axonal stumps of the severed axons. This is followed, two days later, by an increase in dopamine throughout the ganglia, suggesting that dopaminergic cells begin to proliferate at the time. The dopaminergic cells may be responding to stimuli resulting from degeneration of cells in the ganglia and forming new axonal sprouts.

Section on Histopharmacology
David M. Jacobowitz, Ph.D., Chief

The Section on Histopharmacology uses the techniques of histology to localize biogenic amines in brain, to trace pathways of the aminergic neurones, and to correlate biochemical or electrolyte lesions in one area of brain with biochemical alterations in other areas, with behavioral changes, and with alterations in the effects of drugs. Many of these studies are carried out in collaboration with investigators in other sections of the Laboratory of Clinical Science or Divisions of N.I.H.

Histochemical and biochemical mapping of noradrenergic neuronal pathways has been accomplished by the use of a neurotoxic agent, 6-hydroxydopa, and by stereotaxic placement of brain lesions. These procedures have revealed discrete pathways to individual regions of the brain (hippocampus, septum, cortex, amygdala, hypothalamus, thalamus). With Dr. Kobayashi, lesions of the locus coeruleus have been correlated with biochemical assays of catecholamines in small nuclei of the brain. The paraventricular and periventricular nuclei and the habenulae nuclei of the diencephalon receive a major noradrenergic contribution from the locus coeruleus. Cortical noradrenergic nerves, however, are not solely derived from the locus coeruleus cell bodies. In addition, crossover of noradrenergic nerves was shown to take place at the posterior

commissure to innervate the colliculi and geniculate bodies.

A complete brain atlas of the localization of noradrenergic and dopaminergic terminals and cell bodies, in addition to acetylcholinesterase-containing neurons, of the rat brain has been prepared. Currently a similar mapping of aminergic neurons and serotonergic cell bodies in the monkey brain is being prepared.

The increased "emotionality" observed in rats treated with 6-hydroxydopamine to reduce brain norepinephrine is markedly attenuated when 5-HT is simultaneously reduced by treatment with 5,6-dihydroxytryptamine. Thus, increased "emotionality" following reduction of brain norepinephrine might be due to a relative predominance of serotonin in the norepinephrine-serotonin balance which underlies "emotional" tone.

Gold-thioglucose, a drug capable of destroying cells in the ventromedial nucleus of the mouse brain was shown to specifically deplete the median eminence of catecholamines without destruction of the dopaminergic neurons of the arcuate nucleus.

A unilateral injection of 6-OHDA into the brain of rats, which prevented the hypertension produced by DOCA-salt treatment of uninephrectomized rats, results in a unilateral destruction of the nigrostriatal dopaminergic system.

Placement of vinblastine to block axonal transport in the ventral cholinergic pathway was used to demonstrate that the dorsolateral tegmental nucleus was an important nucleus of origin of this tract.

Superior cervical ganglion cells of newborn rats implanted within the lateral ventricles of adult rats have been shown to survive and maintain their catecholamine content, as revealed by fluorescence microscopy.

Superior cervical ganglia grown in culture by Dr. Webb have a greater rate of dopamine than norepinephrine synthesis. Ganglia maintained in culture for over two weeks show complete destruction of adrenergic cell bodies while chromaffin cells survive and contain small amounts of dopamine but essentially no norepinephrine. These studies support the fact that chromaffin cells of the rat superior cervical ganglion contain dopamine and suggest that dopamine-containing fibers sprout during the early stages of organ culture. Immunofluorescence studies using an antibody to DBH, however, revealed that the chromaffin cells of the guinea pig

coeliac ganglion contains DBH while that of the SCG do not. This indicates that the extra-adrenal chromaffin cell amine content of DBH probably varies, depending on individual ganglion localization.

Using fluorescent-labelled antibodies to DBH it has been found that after removal of the superior cervical ganglion of rats, extra-neuronal deposits of DBH are localized within the acinar lumen of the sublingual but not the submaxillary salivary gland.

Section on Psychiatry
Dr. Frederick Goodwin, M.D., Chief

The program of the Section on Psychiatry includes both clinical descriptive studies and biologic investigations involving pharmacological alterations of biogenic amine metabolism, transport of amine metabolites, and effects of amines on endocrine states.

Clinical studies of patients with mental disturbances have identified specific characteristics which are not only useful in reliably differentiating schizophrenic, schizo-affective, and manic-depressive subjects, but which may be of predictive value in assessing outcome. In manic-depressive patients, age of onset has been found to be related to certain clinical features, response to therapy, and long-term prognosis.

In "psychodynamic" studies employing traditional constructs (ego functions, defensive mechanisms, etc.), psychodynamic changes in patients with affective illness, particularly during periods of rapid symptomatic change secondary to drug treatment, have been examined. All 20 patients studied showed clinical evidence of a strikingly similar constellation of unconscious conflicts centering around chronically and massively impoverished relationships, the denial of feeling about this ("negative insight") and the breakdown of this defensive system prior to depressive or manic episodes. Drugs appear to facilitate the reestablishment of more resilient defensive patterns. A separate study of the marriages of manic-depressive patients uses a working couples group as a data source.

Pharmacological blockade by probenecid of transport of metabolites of biogenic amines from the cerebrospinal fluid to the blood has been used to assess the rate of metabolism of amines in brain. Such studies have been extended, in collaboration with investigators in the Adult Psychiatry Branch, to include patients with schizophrenia. A sub-group of patients with affective illness who have low CSF MHPG during depression continue to have low values in the recovery period immediately preceding discharge. Another sub-group of depressed patients with low 5HIAA accumulation on

probenecid has been identified; frequency distribution of the NE and 5HT metabolite data suggests that these are independent variables. In acute schizophrenics MHPG, is in the normal range while the probenecid-induced accumulation of HVA is increased, apparently in association with the acute psychosis.

Interpretation of studies of urinary amine metabolites in manic-depressive patients has required extension to normal control subjects. Moderate degrees of physical activity caused a 100% increase in urinary MHPG in depressed patients but not in controls in normal subjects. An experimental stress situation (pain) produces a slight increase in MHPG during the stress; the increase correlated positively with depression scores on the MMPI (r=.89). Preliminary evidence suggests that compared to normal subjects, depressed patients have a larger increase in MHPG during stress. Before treatment urinary MHPG in depressed patients appears to be of predictive value in determining the clinical response to amitriptyline or imipramine; unequivocal amitriptyline responders had high pretreatment MHPG compared to clear non-responders, whereas the reverse was true for imipramine. There was no overlap in the individual values between the responder and non-responder group for either drug.

Changes in levels of plasma growth hormone and prolactin following oral administration of L-DOPA are used as an indirect method of evaluating the functional capacity of central catecholamine systems. In seven depressed patients, preliminary data suggests that compared to normal subjects these patients have a decreased growth hormone response to L-DOPA. Furthermore, administration of a dopamine-β-hydroxylase inhibitor (Fusaric Acid) to manic patients decreases the growth hormone response to L-DOPA. Lithium administration was found to be associated with a decreased TSH response to TRH, indicating a possible hypothalmic locus for at least some of the antithyroid effects of lithium.

Fusaric acid, a potent and specific dopamine-β-hydroxylase inhibitor, had no beneficial effects in mania and in fact, in those patients whose mania was characterized by psychotic features, there was an intensification of these features while on fusaric acid. This DBH inhibitor is currently being explored as a model to examine the hypothesis that there is a deficiency of DBH in schizophrenia.

Seven depressed patients who did not respond to treatment with tricyclic antidepressants were made sensitive to these drugs by administration of tri-iodothyronine (T-3). These observations

are consistent with earlier work reported by Prange, that T-3 accelerates the response of depressed patients to these drugs. In a trial with nine depressed patients, thyroid releasing hormone (TRH) was found not to be of any significant benefit.

Section on Clinical Neuropharmacology
Dennis L. Murphy, M.D., Chief

The Section on Clinical Neuropharmacology, which was established from a unit formerly within the Section on Psychiatry, will continue both clinical and laboratory investigations in an integrated approach to explain drug-induced changes in human behavior in terms of their biological effects.

To elucidate individual differences in drug response and possible mechanisms of action of psychoactive drugs, the platelet has been used as a neuronal model. This model permits studies at a cellular level in Man. Treatment with lithium carbonate is associated with reduced platelet receptor (adenyl cyclase) responses to prostaglandin E_1 and norepinephrine. Cellular cyclic AMP changes produced by these hormones are also altered in vitro in a dose-dependent fashion, although somewhat greater lithium concentrations are required. Lithium appears to block other hormones which act via cyclic AMP, and these effects may provide alternative or additional (besides lithium's biogenic amine interactions) explanations for some of the psychoactive actions and side effects of lithium treatment. Drs. Costa and Reese, using the platelet model, estimated the size of the serotonin storage packet in human platelets utilizing an electron microscopic approach.

The occurrence of octopamine in human cells was demonstrated for the first time. Although small amounts of this amine, which may function as a "false neurotransmitter," has been found in human urine, and preliminary studies indicated only trace amounts in normal individuals, much larger amounts were positively identified in platelets from depressed patients receiving MAO-inhibiting drugs.

Studies of human monoamine oxidase have continued in two major areas in a large number of normal individuals factors such as age, sex, and hormonal status, including the menstrual cycle, have been verified as being capable of affecting platelet MAO activity. In addition, in vitro studies with multiple subtrates and inhibitors (as well as other approaches) have identified the human platelet MAO as a Type B which is distinct from human plasma MAO. Platelet MAO appears very similar, if not identical, to the B component of MAO found in other tissues, including brain.

The effects of drugs on behavior and memory function have been examined and related to pre-existing personality. Patients with bipolar depression, whether depressed or manic, are moderately improved by treatment with L-tryptophan, while unipolar patients are little affected by this drug. However, L-tryptophan had an enhancing effect on verbal learning in all of the patients. The memory-enhancing effects of L-DOPA were found to depend on long-term, high dosage treatment. Neither learning nor behavioral changes occurred during intravenous administration of L-DOPA to depressed patients pretreated with MK-486. With Drs. Henry and Buchsbaum it was found that there is a definite cortical evoked response alteration after intravenous administration of L-DOPA.

An extension of some studies carried out by Dr. Donnelly have confirmed earlier findings of large differences between bipolar and unipolar depressed patients on MMPI subscales, on Rorschach responses, and on other psychological tests. In a study, carried out with Dr. van Kammen, differential effects of D- vs L-amphetamine have been obtained and are being examined to determine whether amphetamine responses are predictive of the efficacy of tricyclic antidepressant effects in these patients.

Section on Experimental Therapeutics
Dr. Thomas Chase, M.D., Chief

Clinical investigations of the relationship of central dopaminergic mechanisms to the pathogenesis of extrapyramidal dysfunction and to the mechanism of action of L-DOPA have made use of newly available dopamine receptor agonists. One such drug, ET-495, improved parkinsonian signs, although only about half as much as did L-DOPA. As expected of a dopamine agonist, ET-495 markedly reduced central dopamine turnover as estimated by the oral probenecid loading technique. The foregoing results suggest that ET-495 may act in man only as a partial dopamine receptor agonist. In support of this possibility is the observation that ET-495 suppresses involuntary movements in some patients with tardive dyskinesias, an extrapyramidal syndrome believed to reflect denervation supersensitivity of striatal dopaminergic receptors.

Several clinical pharmacological studies have attempted to elucidate the role of noradrenergic systems in the pathogenesis of Parkinson's disease and in the mechanism of action of L-DOPA. Fusaric acid, a potent dopamine-β-hydroxylase inhibitor, at doses which appeared to significantly decrease central norepinephrine synthesis, failed to alter parkinsonian severity in otherwise untreated patients or to modify the ability of L-DOPA to ameliorate parkinsonian signs or induce dyskinesias. The β-adrenergic blocking agent, propranolol, also had no effect on the clinical response to L-DOPA in a small number of parkinsonian patients. Although clonidine, a suspected α-adrenergic agonist, acts in the experimental animal to potentiate the motor effects of ET-495, the

opposite results have been found in parkinsonian patients studied thus far.

A study of the effect of diet on brain serotonin metabolism, completed in collaboration with Drs. J. Perez-Cruet and D. L. Murphy, indicates that there is an inverse relationship between total plasma levels of the serotonin precursor, tryptophan, and the spinal fluid content of this amino acid as well as of the serotonin metabolite, 5-hydroxyindoleacetic acid. Our results suggest that serotonin formation in brain may depend on such factors as the binding of tryptophan to plasma proteins, the level of plasma triglycerides, and levels of other neutral amino acids which compete with tryptophan for transport into the central nervous system.

Evidence that serotonin-mediated systems may play a role in certain human behavioral activities derives from recent studies with fenfluramine. Treatment with this agent, which is known to facilitate serotonergic function in the experimental animal, significantly reduced food consumption and increased both somnolence and depression. As expected of a drug which may block serotonin reuptake or stimulate postsynaptic serotonin receptors, a substantial decline in central serotonin turnover occurred in all patients receiving fenfluramine.

Recent reports of markedly reduced brain GABA levels in patients with Huntington's disease have prompted therapeutic trials of suspected GABA receptor agonists. Neither imidazole acetic acid nor the p-chlorophenyl derivative of GABA (Ba 34,647) were found to significantly modify involuntary movements in choreatic patients. It remains to be determined whether this result is due to pharmacokinetic factors or to an inherent inability of GABA replacement therapy to modify the motor signs of Huntington's disease.

Several hypothalamic releasing factors have been reported to potentiate the motor effects of L-DOPA in the experimental animal. Therapeutic trials of intravenously infused thyrotropin releasing hormone or melanocyte stimulating hormone release inhibiting factor failed, however, to significantly modify extrapyramidal function in otherwise untreated parkinsonian patients or to alter their clinical response to L-DOPA. A therapeutic trial of melanocyte stimulating hormone release inhibiting factor, given orally in very high doses, has now been started on Guam in parkinsonian-dementia patients.

Studies of the ability of monoamine-containing neural systems to influence the release of human pituitary hormones have begun in collaboration with Dr. A. C. Carter. Like L-DOPA, FT-495 was found to depress circulatory prolactin levels but increase plasma concentrations of growth hormone. Fenfluramine, on the other hand,

supressed the release of growth hormone, but lead to a significant rise in prolactin. Neither drug significantly altered TSH, FSH or LH levels. These preliminary results suggest that in Man dopamine- and serotonin-containing neural systems may act reciprocally on the release of certain pituitary hormones.

A controlled study of the analygesic efficacy of acupuncture is now being conducted in normal volunteers together with Dr. M. Buchsbaum. A computerized system allows the amplitude of a random series of electrical stimuli, delivered to one forearm, to be rapidly correlated with patient reports of stimulus intensity and associated alterations in cortical evoked potentials. Thus far no difference has been discerned between the ability of "placebo" and "active" needle placements to modify either the subjective or objective response to stimulation.

Preclinical studies of central cholinergic mechanisms continue. Previous work has shown that lithium chloride diminishes choline uptake into rat brain in vivo. In vitro studies now indicate that lithium ions competitively inhibit the uptake of choline into rat brain synaptosomes, thus diminishing acetylcholine synthesis, but have no effect on the activity of enzymes mediating the synthesis or degradation of acetylcholine or on the electrically-induced release of this presumptive neurotransmitter. During the past year pharmacologic and radioisotopic methods for estimating central GABA turnover have been developed. Neither acute nor chronic L-DOPA treatment altered the metabolism of this suspected neuromediator.

Office of the Chief
Irwin J. Kopin, M.D., Chief

Dr. Michael Ebert, Head, Unit on Clinical Pharmacology, uses a technique for continuous collection of cerebrospinal fluid from the cerebral ventricles of monkeys, preliminary studies have indicated that homovanillic acid is rapidly formed from deuterium labelled methionine. With development of a method for assay of the specific activities of methionine and HVA the rate of formation of the metabolite can be quantitatively assessed and used as an index of the rate of dopamine metabolism. Other studies are directed towards assessing the rate of norepinephrine metabolism in brain using its major metabolite, MHPG.

Dr. Robert Colburn, Head, Unit on Analytical Biochemistry, has continued his studies on amine uptake, release, and metabolism in synaptosomes isolated from rat brain. Scorpion toxin was found to induce a partially calcium-dependent release of norepinephrine. The mechanism of release appears to be similar to that produced by depolarizing agents or sympathomimetic amines since the deaminated products are not increased as they are after reserpine-induced amine depletion. Tetrahydrocannabinol, but not its metabolites, are concentrated in synaptosomes largely because of

the lipophilic properties of the drug rather than any active transport process. Drs. Hawks and Colburn have found that cocaine and its demethylated derivative, narcocaine, equipotent in inhibiting amine uptake by synaptosomes, but other cocaine metabolites are inactive.

Dr. Hawks has synthesized a variety of potential metabolites of cocaine and has identified some of them in the plasma and urine of patients treated with cocaine. A study on the pharmacodynamics of cocaine in Man is the subject of a collaborative project with Dr. Post of the Adult Psychiatry Branch.

The Unit on Clinical Biochemistry, headed by Mrs. Edna Gordon, performs the biochemical analysis of neurotransmitter amines and their metabolites. Studies have been undertaken to correlate changes in behavior, affective states, progress in recovery from mental illness and response to drug treatments with changes in concentration, metabolism and turnover rates of these compounds. Studies involving patients have been done in collaboration with the Sections on Psychiatry and Experimental Therapeutics and the Adult Psychiatry Branch.

Dopamine (DA) and norepinephrine (NE) are the amines which are being studied most intensively because theories suggest their involvement in schizophrenia and depression. To analyze cerebrospinal fluid (CSF) more sensitively and reliably, a method using the gas chromatograph-mass spectrometer has been developed to measure simultaneously homovanillic acid (HVA) (the main dopamine metabolites), vanillyl mandelic acid (VMA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) the main norepinephrine metabolites. Determinations have been made on numerous samples of human CSF, and the results are being analyzed. Preliminary results indicate that in brain NE metabolism results in formation of much more MHPG than VMA. Additional analysis is necessary to assess changes in relative amounts of the 3 compounds under different conditions of treatment.

In order to get more basic information on the metabolism of DA and NE in brain and the transport of the metabolites out of that tissue, samples of CSF have been obtained from the lateral, third, and fourth ventricles of monkeys and from the cisternal and lumbar regions. Results show that the concentration of metabolites in the CSF reflects the concentrations of the precursor amines in the surrounding areas of the brain. The caudate nucleus has high concentrations of dopamine, and this is reflected by the highest concentrations of HVA found in CSF obtained from the lateral ventricles. The hypothalamus has a higher concentration of NE than the cortex. The concentration of MHPG in the CSF from the third and fourth ventricles, which are nearer this area, was found to be approximately twice that of the lateral ventricles. These observations confirm and extend previous studies of HVA in spinal fluid.

The methods of mass fragmentography make possible the use of compounds labelled with stable isotopes as tracers. Procedures are, therefore, being developed to include analyses of metabolites in blood. The use of stable rather than radioactive isotopes and analysis of blood rather than CSF should extend the possibilities for studies of these neurotransmitters in humans.

ANNUAL REPORT OF THE LABORATORY OF CLINICAL PSYCHOBIOLOGY
National Institute of Mental Health
July 1, 1973 - June 30, 1974

Frederick Snyder, M.D., Chief

This is the last annual report of the Laboratory of Clinical Psychobiology, since the impending reorganization of DCBR during the coming year will involve its disestablishment. Created at my instigation in 1968, when it seemed that personal energies were as limitless as institutional resources, changing circumstances over the past 6 years have taken a heavy toll of both. Despite progressive reduction of our staff during that time, much of what we set out to do has been either accomplished or well begun, together with much more not then envisioned. For that I am grateful to the small handful of exceptional young researchers who have shared my efforts. Most of those have now gone on to continue our work elsewhere however, and this no longer so young researcher also feels the need for new horizons and challenges.

Although a few new lines of work have been ventured during the past year, the main goals of our small remaining staff have been to complete older studies, some of them extending back over many years. Thus, we are still struggling to finish the prodigous task of sleep record scoring and analysis from longitudinal studies of various psychiatric patient groups -- just one of the masochistic facets of clinical sleep research. The nearest of these to publication is a series of 6 longitudinal case studies bearing upon the question of sleep changes during transient episodes of mania.

As we have previously found in acute schizophrenic or depressive illnesses, the overall extent of sleep loss in mania roughly reflects the degree of behavioral disturbance and involves disporportionate loss of REM and delta sleep patterns. Several of these cases displayed an interesting form of sleep disorder, not previously noted in any other condition, involving nights of little or no sleep alternating with nights of longer than normal sleep. To whatever extent we can succeed in the time remaining to extract graphs and numbers from our mountains of paper records, we shall also have extensive additional data about alterations in sleep in the course of depressive and schizophrenic conditions and how these are influenced by various therapeutic modalities.

A much more circumscribed study has now been completed on the sleep patterns and psychological characteristics of people with long-standing complaints of insomnia in the absence of other discernible organic or psychiatric problems, the primary insomniacs. One of the first studies of that group adequately controlled by comparison with age-matched subjects, our data does reveal a modest overall reduction of sleep and

particular deficiency of deeper sleep, yet goes little further than previous reports in explaining the degree of anguish such patients voice about their sleep. Whether cause or effect of their sleep problems, average evoked response data of our primary insomniacs reveal lower evoked responses to sound (they are sensory reducers), while psychological test results indicate greater depression and anxiety as well as less proficiency in perceptual motor skills.

Whatever else may be wrong with them, our studies agree with most previous ones that primary insomniacs do have difficulty getting to sleep. Therefore, we have begun formal therapeutic trials of several approaches intended to help insomniacs achieve states of muscular relaxation, one involving the use of electromyographic feedback, and the other a combination of meditation and self-hypnosis widely used in Europe under the name "autogenic therapy." Although pre- and post-treatment sleep patterns or psychological test data have not yet been completely analysed, the subjects' subjective reports about effects of these procedures on their insomnia are moderately encouraging.

The use of biofeedback in treatment of insomniacs has fired the interest of several staff members in biofeedback itself, the process by which we can learn to control voluntarily specific physiologic functions ordinarily considered to be outside of conscious, voluntary control. On the one hand, we are concerned with methodological issues such as how the process may be affected by the nature of the feedback stimulus or the manner in which it is processed, and on the other hand with the potential usefulness of this approach as treatment. Pilot efforts are in progress to help patients with chronic tension or migraine headaches or essential hypertension by teaching them to relax their frontalis muscles or to raise their finger temperatures. There is hope at present that this work may be carried on by Dr. Frankel under the sponsorship of the National Heart and Lung Institute after our own program is brought to a close.

We are happy to see the end in sight for 2 especially arduous sleep studies, the one undertaken by our guest nurse researcher, Evelyn Elwell, to examine the nature of sleep disturbance after open-heart surgery, and the other by Rona Buchbinder to clarify whether there are normal variations in sleep associated with the menstrual cycle. In the face of formidable obstacles and frustrations, Ms. Elwell has successfully completed her studies on 5 cardiotomy patients and is well advanced in analysis of the data. For the first time, this objectively and quantitatively documents just how severe and long lasting the disruption of sleep is following such drastic surgery, and undoubtedly has implications for the serious psychiatric disturbances often ensuing. While no less hard won, the extensive menstrual cycle data will be more difficult to interpret, since it appears from their temperature charts that 4 of the 6 women studied perversely failed to ovulate during those cycles when their sleep was recorded! To make the best of

misfortune, however, we hope to use this data and that from the 2 male controls studied in the same fashion in order to examine the degree of normal intra-individual variability of nightly sleep patterns in the absence of the possibly confounding influence of ovulation.

The biochemical, pharmacological and endocrine studies of sleep so vigorously pursued here a few years ago have been largely transferred to Dr. Richard J. Wyatt's Laboratory of Clinical Psychopharmacology at St. Elizabeths Hospital, yet we continue to collaborate with him and his colleagues on special projects more easily undertaken here. An old study on the possible role of histamine in sleep-waking mechanisms has been completed and is awaiting publication, as has another on differential effects of d- and l-amphetamine on sleep patterns. In the meantime, Drs. Gillin and Frankel have begun to explore the possible role of cholinergic influences on the occurrence of REM sleep attacks in narcolepsy; they have some preliminary evidence that the cholinergic blocking agent, Artane, tends to alleviate narcoleptic attacks, but have been unable to show that physostigmine aggravates them. Suitable narcoleptic patients for such trials are rather few and far between but Dr. Gillin can be counted on to gradually extend the present small series.

Within our small Section on Comparative Studies, Dr. Douthitt has completed his fruitful collaborations with Drs. Perez-Cruet and Brackbill on the effects of 6-hydroxydopamine on the development of arousal responses in young rats. The provocative finding was that brain norepinephrine depletion was not reflected in diminished arousal responses to stimulation until 28 days of development when adult levels of norepinephrine are normally approached. As detailed in last year's report, Drs. Douthitt and Perez-Cruet have now also concluded our brief tradition of work on the psychobiology of aggression in the rat begun in 1970 by Dr. Burr S. Eichelman.

Finally, I must account for my solo research efforts during the past year while on a foreign work assignment as Visiting Professor of Psychiatry at the University of Nairobi in Kenya. Since my teaching duties were light, I had considerable time left over to pursue a long-standing obsession for learning about the nature of sleep in all kinds of animals, and just happened to have brought along equipment to do this by 2 alternative approaches. The one was the implantable EEG telemetry device developed here in our comparative laboratory and suitable for short-range studies of small, captive animals. The other was a longer range telemetry system especially designed by Mr. Jim Bryan, formerly Chief of Section on Technical Development, for the purpose of attempting to record EEG sleep-waking patterns from larger, free-roaming animals in their natural habitats, something never before accomplished.

I shall not dwell on either the immense personal gratifications of that experience or upon the almost equally great difficulties and frustrations of trying to initiate such projects (or just learning to live), in a strange and underdeveloped country. Much time and effort went into

obtaining animal specimens, maintaining them in captivity, and building appropriate outdoor enclosures, to say nothing of trying to keep recording equipment and transport functioning. By the same token, over half of the allotted year was gone before a suitable situation could be found where it was possible to attempt the free-roaming animal project, and additional months were lost because of seasonal rains making bush travel impossible. Out of necessity, therefore, the captive mammal studies became the primary project (although it was not the primary challenge) while field trials on free-roaming zebra became a secondary, sporadic activity, interspersed when time, weather conditions, and the willingness of my family member assistants permitted.

Since complete 24-hour records of the zebra never were successfully obtained for reasons detailed in this report, the chief gain in that area was sobering experience as to the probable investment which would be required for success in terms of suitable telemetry equipment, human skills, energies and time. By contrast, the telemetry studies of small captive mammals, although laborious, were highly successful and productive. Very adequate records were obtained for characterizing the sleep-waking patterns of 7 species, together with exploratory studies of 4 more--none ever previously investigated from this standpoint. When finally processed and analyzed the voluminous data should amount to a very significant contribution to our still scant knowledge of how variations in sleep relate to diverse mammalian adaptations. Aside from its relevance to sleep science itself, however, the hyrax findings described in the comparative studies project report amount to an entirely new concept of that group's particular behavioral ecology.

It has often been observed that the kinds of people needed to pioneer in various human endeavors are typically quite different in abilities and temperament from those later needed to colonize and develop them to their ultimate harvest. I am most grateful to the National Institute of Mental Health and to the Intramural Research Program for granting me the freedom and support over the past 17 years to stumble about, explore, and hopefully to pioneer on a most challenging and exciting frontier of human knowledge. Since that frontier has now become a busy and well-established field of science, it is time to move on.

Annual Report of the Laboratory of Psychology

National Institute of Mental Health

David Rosenthal, Ph.D., Chief

July 1, 1973 - June 30, 1974

As with the case of other parts of the IRP, the Laboratory of Psychology has been involved with problems and issues of reorganization during the past year, and has considered the possibility of reorganizing itself in different ways. These will be spelled out in a future report. During the past year, the Laboratory lost one of its most productive scientists, Dr. Paul H. Wender, who accepted a professorship elsewhere. Also, Dr. Allen T. Dittmann, after 20 years in the Laboratory, has decided to accept a professorship and will leave in the fall. Dr. John L. Van Dyke, who represents a testimonial to the unique training advantages that young assistants can obtain in the IRP, will leave to take a position elsewhere as an independent scientist.

The research directions and achievements of the Laboratory during the past year may be summarized as follows:

Brain Function and Behavior in Primates

Brain Regions in Stimulus-Reward Associations.

Previous evidence gathered by this Laboratory points to the temporal pole and amygdala as the limbic region that probably contributes most to the establishment of stimulus-reward associations, but leaves open the question of whether that function depends on the anatomical connections with the inferotemporal area. To study the question, a "crossed-lesion" experiment has been undertaken that is similar in principle to the one with which we first demonstrated the functional role of the striate-inferotemporal connections. The design involves removing the inferotemporal cortex from one hemisphere, the temporal pole and amygdala from the other, and then cutting the forebrain commissures. The commissurotomy should disconnect and isolate the intact temporal pole and amygdala on one side from the intact inferotemporal cortex on the other side and thus produce a functional bilateral ablation of the temporal pole and amygdala. The test of this prediction is whether or not animals with such lesions will perform as poorly as those with actual bilateral ablation of the temporal pole and amygdala. Preliminary results indicate that this is indeed the case, and further, as might be expected from the anatomy of the temporal lobes, that cutting the anterior commissure alone in animals with the crossed lesions is sufficient to produce the reversal learning impairment.

To determine directly whether the temporal pole and amygdala are involved in the establishment of stimulus-reward associations, the activity of single units in these areas will be measured while an animal performs on visual discrimination reversal. Two grossly dissimilar stimuli, A and B, will be presented in random succession, and the animal will be trained first with A the rewarded stimulus in the pair, then with B the rewarded stimulus, and

so on through a series of discrimination reversals. Positive evidence for our hypothesis would be provided by a finding that the discharge frequency of a given unit depends on the reward value of the stimulus (A+ vs A-) and not on its sensory quality (A vs B). The converse results, i.e., sensitivity to the sensory and not to the affective quality of the stimulus, would be expected of units in the inferotemporal area, for according to the present model this tissue is an intrinsic part of the visual system.

Frontal Cortical Mechanisms in Spatially Directed Responding.

Although previous studies in this laboratory have emphasized behavioral analysis following selective lesions, current research is directed toward exploring the usefulness of other concepts and techniques as they bear upon mechanisms underlying behavior. For example, while a great deal is known about the functions and anatomical connections of the prefrontal cortex, almost nothing is known about the neurochemical properties of this region or how these may relate to behavior. Do the anatomical pathways to and from the prefrontal cortex involve selective neurochemical transmitters? Can the major functional subdivisions of the prefrontal cortex be differentiated in terms of different neurochemical pathways? Does injury to the prefrontal cortex result in disturbance in metabolic function in regions remote to the injury, for example the caudate nucleus or the hypothalamus? If so, are these effects slighter if the damage is sustained in infancy or in stages, conditions of injury associated with greater recovery of function? These and other questions are concerned with elucidating the relationship between the physiology, anatomy, and biochemistry of the neural substrates of behavior. Last year, together with Dr. J. Perez-Cruet of the Laboratory of Clinical Sciences, we began to explore these questions. An initial investigation sought to determine the effects of dorsolateral and orbital prefrontal lesions on the metabolism of biogenic amines in various regions of the central nervous system. All data for this study have been collected and are now being analyzed. Preliminary results suggest that the cortical lesions produce widespread metabolic effects and that an important and fruitful line of investigation has been opened.

Together with Drs. Popper and Havens, also of the Laboratory of Clinical Sciences, we have initiated a complementary investigation employing pharmacological techniques. Although the psychoactive effect of many drugs is plainly evident, it is rarely clear where in the brain such drugs may be acting to alter behavior. Approaches to the problem of local action that involve either systemic or intraventricular injection of drugs are inadequate in that regional specificity cannot be claimed. In our studies, bilateral cannulas have been implanted directly over specified regions of the frontal cortex in monkeys trained to perform delayed alternation and visual discrimination problems. By injecting radio-opaque dyes through such cannulas in untrained monkeys, we have determined that the distribution of compounds injected through the cannulas is restricted to the target region -- thus establishing the feasibility of local injections. We will examine the effect of five putative neurotransmitters on behaviors that depend upon the integrity of prefrontal neurons. If specific effects are obtained for particular agents, these will be candidates for more analytic studies involving the action of antagonists and the effects of drugs which potentiate or inhibit neural transmission.

These studies may shed light on the neurochemical pathways involved in frontal-[illegible] and also provide a means of elucidating how drugs administered systemically can affect behavior by acting on specific regions of the brain.

Cerebral Mechanisms for Functional Recovery After Brain Injury.

Many studies on adult monkeys described elsewnere in this report (e.g., neurochemical and anatomical studies) are relevant to the question of neural development and plasticity because they establish the status of the adult nervous system against which manipulations at early ages can be compared. In this section of the report, however, we discuss only those studies involving infant monkeys directly.

The ablation technique can be used to determine what functions are mediated by what structures. Previous research on infant monkeys, however, has established that this technique can also be used to determine when in development these functions arise. For example, previous research in this laboratory has provided evidence that subcortical structures mediate behavior long before the cortical areas, with which they are anatomically associated, come into play. The changing importance of anatomical entities with age was clearly illustrated by the findings that at early stages of development, lesions of the caudate nucleus produce more severe deficits than do lesions of the dorsolateral cortex, while at maturity, conversely, lesions of the dorsolateral cortex produce more severe impairments than lesions of the caudate.

Research during the past year has amplified and extended our analysis of cortical development. Earlier studies had involved removing the dorsolateral or orbital prefrontal cortex in infancy, testing the monkeys when they were one year of age and, finally, retesting them at two years of age. Monkeys with orbital lesions were impaired at the one-year stage of development but deficits in monkeys raised from infancy without their dorsolateral cortex were not evident until two years of age. These findings suggested that the orbital prefrontal cortex became committed to its functions at a considerably earlier age (one year) than did the dorsolateral cortex (two years of age). In current research, monkeys that had been given dorsolateral prefrontal lesions in infancy (as before) were tested for the first time when they were two years old. As in previous studies, the monkeys were impaired at two years of age in spite of the fact that their lesions had been incurred in infancy. These findings extend the evidence for the late development of the dorsolateral cortex and, in addition, impose restrictions on the degree of plasticity that has been claimed for the immature nervous system.

Although previous studies indicated that the functions of the orbital cortex were well developed by one year of age, they did not provide evidence on how early within the first year of life such functions were present. While the study mentioned above employed the strategy of assessing the effects of dorsolateral injury at later and later stages of development, another study adopted the opposite maneuver in regard to orbital function, i.e., constricting the period of assessment into the first six months of life. Monkeys given orbital lesions in infancy (50 days of age) were first tested at 2 1/2 months of age or at 6 months of age. So far, only the 2 1/2 month data have been

analyzed but these data indicate that the orbital cortex may be functional in some animals at this early age. Thus, it would appear that there is a time lag of nearly two years between the functional development of the orbital prefrontal cortex and that of the dorsolateral prefrontal cortex. Differences of this magnitude in the timetables for maturation of specific regions of the cerebral cortex provide an important opportunity for the analysis of structure-function relationships in development.

The evidence for the late development of the dorsolateral cortex tells us something not only about the normal sequence of brain development, it also helps to understand mechanisms of recovery of function following certain early brain injuries. We have now clear-cut evidence that monkeys raised from infancy without the orbital prefrontal cortex are impaired when initially tested at 2-1/2 or 12 months of age. However, in spite of their initial deficits (which establish the functional maturity of the orbital cortex at early ages) these monkeys exhibit considerable "recovery" of function when they are retested at two years of age. Evidence obtained last year indicates that the recovery phenomenon depends on the integrity of the dorsolateral cortex and on the opportunity for experience during development. If the dorsolateral cortex is removed along with the orbital cortex in infancy or if the dorsolateral cortex is removed at two years of age, the recovery is abolished. If monkeys are raised from infancy without orbital prefrontal cortex and are initially tested at two years of age without benefit of prior experience, recovery is also abolished. Our evidence suggests that as long as orbital damage occurs in infancy, the dorsolateral cortex develops normally and experiential factors aid in this development. The "recovery" exhibited by monkeys with orbital lesions sustained in infancy is thus viewed as the emergence with age of new capacities added by the normal development of intact structures rather than the expression of unusual plasticity.

Studies of infant monkeys continue to turn up new and unexpected findings. Last year, as a result of accumulating a large number of cases under a variety of conditions, we discovered that orbital lesions in infancy produce deficits in males at 2-1/2, 12, 18 and 24 months of age while comparable deficits in operated female monkeys could not be detected until 18 months of age. These results provide evidence that the orbital cortex develops earlier in males than in females. Evidence for functional dimorphism in neocortical substrates is an unprecedented finding of considerable interest. A sex-related difference in the development of cortical regions could have major implications for the organization of cognitive behavior during the formative years and quite possibly for behavioral differences that outlast these years. These findings also raise the possibility that timetables for the development of the orbital cortex may be influenced by gonadal hormones at critical periods in development. Current research is directed toward examining this possibility.

Finally, a new area of investigation entered upon last year in collaboration with investigators at Bionetics and I.B.R., involved surgical manipulation of the primate fetus. One rhesus monkey fetus given a dorsolateral prefrontal lesion at 100 days of gestation was replaced in utero and delivered successfully at term (168 days of age) by cesarean section.

Another case was successfully delivered but succumbed from a respiratory infection several weeks after birth. Seven other monkeys operated upon prenatally were aborted within a few days after surgery. The project has been temporarily suspended due to the high cost in time and effort. However, the surviving monkey, a healthy animal with no apparent sensory or motor defects, who cannot be differentiated from other young monkeys in this laboratory on the basis of unlearned behavior, is now being studied intensively. After behavioral measures are complete (when the monkey reaches 2 years of age), anatomical studies will be carried out.

Anatomical Correlates of Development and Plasticity.

We are seeking to determine when in ontogeny the dorsolateral and orbital prefrontal cortical areas establish connections with subcortical structures like the caudate nucleus. Monkeys that have received selective unilateral cortical ablations at various stages of development (2 months, 6 months, 24 months) have been sacrificed and their brains processed with silver impregnation techniques to determine the status of cortical-subcortical pathways at the different stages of development. Preliminary evidence that degenerating fibers are not present following either lesion at 2 months of age but are present by 6 months of age suggests that the cortico-striatal pathway is either immature or not present at the two-month stage of development. Other techniques such as autoradiography and horseradish peroxidase are planned as adjuncts to the silver methods.

Monkeys which have been given bilateral orbital prefrontal lesions as infants will be allowed to mature and behavioral data will be collected at maturity to insure that functional recovery has occurred. At this time, unilateral cortical lesions will be placed in areas suspected of mediating recovery, and silver impregnation techniques will be employed to determine if there has been any alteration or elaboration of intact pathways (collateral sprouting) that could mediate the behavioral recovery.

Somatosensory Processes.

Our experiments have shown that lesions of the postcentral gyrus (Somatosensory area I, or SI, delineated by Woolsey electrophysiologically) produce severe impairments on most tests involving somatosensory discriminations with the hand (monkey). These impairments turned out to be ascribable mainly to destruction of the posterior bank of the central sulcus, a conclusion which emerges strikingly from our results and finally brings the behavioral data into harmony with the anatomical fact that this area receives the bulk of the thalamic projections from the main somatosensory relay nucleus.

This year we have obtained further behavioral evidence that is in accord with anatomical knowledge of the sensory areas but contrary to the behavioral results reported previously by others. For many years, Somatosensory area II, or SII of Woolsey, has posed a problem, since no deficits of any kind seemed to follow its removal, despite the well-organized sensory projection it receives. We have recently been able to show that such a removal does cause deficit in somatosensory discrimination tasks, and there are

some interesting differences between this deficit and that following removal of SI: 1) a bilateral lesion of SII is necessary to produce a serious impairment, whereas a unilateral lesion of SI suffices--this finding fits with the bilateral projection to SII and the predominantly contralateral projection to SI: 2) the impairment is less severe than that following an SI lesion--this finding is what one might expect since SI receives the more abundant projection; and 3) the impairment after an SII lesion does not affect the tasks requiring the most palpatory activity by the subject, whereas these tasks are greatly impaired by SI lesion--this finding is consistent with our expressed interpretation of the primary function of SI as being in "active touch" rather than in refining the perception of passively-received stimuli, the view most commonly held.

Other experiments on the effects of lesions to parts of the parietal lobe behind the postcentral gyrus have indicated that the cytoarchitecturally-defined area 2 of the postcentral gyrus cannot be subdivided into subareas of more and less potency. We have so far been unsuccessful in determining the relation of the selective deficit following area 2 lesion and the apparently similar deficit reported by others to follow lesions of the posterior parietal lesion to obtain the deficit.

We have continued studying temperature discrimination in the effort to find the smallest lesion which will produce a detectable impairment. So far it appears that SI must be removed from both hemispheres, and SII, at least on the side contralateral to the hand tested. Even this lesion produces only a minimal deficit. Temperature (like light touch) perception appears much less vulnerable to cortical lesions than appreciation of consistency, form, size, and roughness.

Schizophrenia

One of the most important recent developments in the concept of schizophrenia involves the principle that schizophrenia may be a syndrome with degrees of gradation in its various symptomatic components. These graded syndromes we call the spectrum of schizophrenic disorders. The concept rests on the hypothesis that the disorders are genetically related. To test this hypothesis, we did the following: First, we obtained adoptees who were now adults, and who had a chronic schizophrenic parent. Then we examined the co-parent with whom the schizophrenic parent mated to produce the index adoptee. We then divided these co-parents into those who had a schizophrenia spectrum disorder and those who had some other behavioral disorder or were normal. Examination of the adopted-away offspring revealed that those adoptees whose co-parents were in the schizophrenia spectrum had a significantly higher frequency of spectrum disorders than did the adoptees whose co-parent was not in the spectrum. Thus, the evidence strongly favors the spectrum concept, and it suggests that past genetic studies of schizophrenia may have failed to come to clear genetic conclusions because, at least in part, not all cases were counted that perhaps should have been.

One member of our Laboratory has evaluated the theory, research, and practice applications of the spectrum concept, and concludes that the spectrum concept (1) draws its theoretical significance from its ability to

simultaneously deal with the two most important problems in psychiatry, no-
[illegible] which roughly
spans the history of the schizophrenia concept itself, and has, at various points in its development, influenced psychiatry, particularly genetic studies; and [illegible] rests on a body of research, being done primarily in this Laboratory, which is capable of developing a nosology of recognized disorders, both psychotic and non-psychotic, which are genetically related to schizophrenia.

However, he also cautions that in clinical diagnostic practice, many problems and some abuses are likely to occur with regard to spectrum diagnosis, at least initially, and he believes that a working diagnostic system based on the concept may not be warranted at the present time.

In an unusually well-controlled high risk study of schizophrenia, we found the following: (1) The offspring of schizophrenics have a significantly higher incidence of perinatal deaths than well-matched controls, even when both groups of mothers received excellent and identical prenatal care; (2) There are more cases of multiple congenital malformations among the offspring of schizophrenics; (3) The deaths and malformations noted above among the offspring of schizophrenics could not be explained on the basis of autopsy findings or adverse conditions of pregnancy, whereas most of such cases in the control group could be so explained; (4) The deaths occurred predominantly among the offspring of parents who were diagnosed as having chronic forms of schizophrenia rather than among those whose parents had acute or borderline forms; (5) The deaths occurred predominantly among those offspring who had schizophrenic mothers, and especially among those who had both parents diagnosed as schizophrenic, rather than among those who had a schizophrenic father only; (6) There was no apparent relationship between the taking of psychotropic medication by the mothers and these deaths; (7) Two other groups, the offspring of parents diagnosed as "possible schizophrenics" and of parents diagnosed with non-schizophrenic diagnoses, did not show an increased rate of perinatal deaths when compared with their matched controls; and (8) Preliminary analyses suggest that the offspring of schizophrenics do not show differences in birthweight or Apgar score when compared with matched controls.

We have previously reported that bipolar affective disorder patients show relatively greater rates of increase of visual AER amplitude with increasing stimulus intensity (augmenting) in comparison with unipolar or schizophrenic patients who often show actual decreases in amplitude (reducing).

Based on a series of studies in both normal subjects and patients, AER augmentation appears to be associated with a tendency to seek excitement and to be insensitive to weak stimuli. Reducing, in contrast, is linked to avoiding excitement, sensitivity to weak stimuli, and pain tolerance.

Recently, correlations between AER scores and individual differences in both pharmocologic response to psychoactive drugs and platelet MAO levels have led to intense investigation of these relationships.

The AER amplitude/intensity slope is negatively correlated with platelet MAO in normal, schizophrenic and unipolar patients. Since both schizophrenics and bipolar patients have low MAO levels and are relatively well differentiated by the AER, whereas unipolars and schizophrenics are reducers but well differentiated by MAO, multivariate analysis was applied. A large group of bipolar, unipolar and schizophrenic patients and 49 normal controls with approximately the same age distribution were used; males and females were analyzed separately. In both sexes, combined classification of the four categories was quite successful with over 72% of the subjects classified correctly; most prominent misclassification errors were normals classed as schizophrenics.

These misclassification errors suggested the possibility of "schizophrenia spectrum disorders" in the normal group. Individuals with both AER reducing and low MAO might be postulated to be at increased high risk for development of schizophrenia, affective illness, or subclinicical symptoms of either.

Acute schizophrenia patients are being tested in procedures which assess the tonic and phasic activity of several peripheral autonomic variables under conditions of rest, mild auditory stimulation, and task performance, and on a test of attention. The tests are done soon after admission, just before discharge, and 6 - 12 months after discharge. Although extensive data analysis has not been done yet it appears that a selective deficit in autonomic responsivity occurring only to more "demanding" situations and stimuli, found previously in more chronic patients, occurs only when the patients are exhibiting moderate to severe schizophrenic symptoms and attentional deficits.

Other Psychopathology

Minimal Brain Dysfunction (MBD) in Children.

MBD children did not differ from normals in autonomic arousal under relatively quiet conditions but they exhibited higher arousal indices under conditions where there was more environmental stimulation. Under both conditions the MBD group showed lowered autonomic responsivity to meaningless stimuli as well as more demanding stimuli. Stimulant drugs, which improved the behavior and attention task performance of the MBD children, raised their arousal levels but not their responsivity to stimuli. The data suggest that MBD children may "need" higher arousal levels for optimal performance than normal children.

The AER is also being used as a predictor of individual response to amphetamine. Among off-medication hyperactive children, we have noted that augmenters with some AER signs of developmental lag respond favorably clinically to amphetamine; AER's change in the reducing direction (toward normal). In contrast, children with reducing and mature AER patterns tend to augment on amphetamine and deteriorate clinically. This finding has led to studies of d- and l-amphetamine in patients with affective disorders. Preliminary results in eleven patients indicate significantly greater effects with l-amphetamine than with d-amphetamine.

Swallowing Disturbances.

Three female patients were examined who experienced an onset of difficulties in swallowing, for which no organic cause could be found, shortly following the death of a parent. Areas of psychological conflict were explored in a series of interviews, and were then discussed while readings of esophageal pressures were simultaneously recorded. The voice and esophageal recordings were compared. The data have not yet been fully analyzed. The following questions are receiving particular attention: (1) Are subjective experiences of swallowing disturbance related to changes in esophageal motility? (2) Do these changes occur within specific psychological contexts, such as sexual or dependency conflicts? (3) If so, do they simply reflect anxiety, or do they occur independently of it or as a consequence of some other affect (such as anger, which might support the clinical impression that these patients exhibit "masked depression")? And (4), if these physiological disturbances do indeed reflect psychological themes and conflicts frequently noted in depression, and if, as has been suggested, minor tranquilizers increase anger, then is the current common use of such agents in these and similar disorders justified, or might other agents, such as the tricyclic antidepressants, or other modalities of treatment, be more appropriate?

Studies of Normal Functioning

Behavioral Development.

Research designs have been formulated to answer experimentally two concurrent questions: (1) Can particular contingent infant behaviors (actual or simulated) function to modify (reinforce) aspects of selected mother behaviors? and (2) What is the effectiveness of selected contingent mother behaviors in modifying features of particular behaviors of her infant? The designs employed are paradigmatic for extensive study of mutual instrumental conditioning of mother and infant, providing considerable flexibility to study the effects of diverse responses of the child (e.g., head turn, leg kick, smiles, laughter, reaching toward) presented contingent on various postural, facial, or verbal responses of the mother.

In the first research phase, we have concentrated on the impact of a simulated set of infant vocalizations on a two-stage response of the mother, a vocal response followed by a smile; and on the influence of the mother's vocal response on the child's response of turning to look at the mother. In the experimental setting, the mother was seated in a lighted room facing a one-way mirror. The infant was in an infant seat on the other side of the mirror in an adjacent, darkened room. The light differential provided the infant with a clear view of his or her mother's face. The mother said a one or two word phrase to her child through a microphone when a sequence of lights was activated by the infant's head turning. Ostensibly, a microphone in the infant's room was automatically activated after the mother finished speaking, permitting her to listen briefly to her child through an intercom positioned near her. In actuality, that intercom received output from a two-channel tape recorder, one channel of ambient noise indicative of the child's silence and one channel of infant vocalizations.

Extensive pilot observations indicated that it would be difficult to condition the responses of the infant and mother simultaneously. We therefore decided to emphasize initially the conditioning of the mother by the infant, and then the mutual conditioning of the mother and the infant. And because the mother's attention span was much longer than the infant's, it was also decided in this initial phase to simulate the infant's headturning response that cued the mother's verbal response. The results reported were obtained from observations of the mother's differential usage of each of six words in a one- or two-word phrase. On the basis of their similiarities of meaning and frequencies of baseline occurrence, these six words were combined into two classes. Each verbal class could be followed by a smile or not followed by a smile, thus constituting four two-phrase response classes: one verbal class with and without smile and the other verbal class with and without smile. During the initial conditioning phase, the verbal class followed by smile that was the lower in baseline incidence occasioned a simulated infant vocalization. The other three response classes were followed by simulated room noise. Following a reliable increase in frequency of the conditioned response class, recorded infant vocalizations were presented contingent on the other response class and room noise followed the previously conditioned response class. These reversal conditions were in effect until a reliable decrease in the frequency of the previously conditioned response class was demonstrated.

We here report the results from over 20 biweekly observations of two mother-infant pairs. These were the first studies under the above-described conditions. The patterns of change from condition to condition in each of these mothers separately are all statistically reliable. For the first mother, the verbal response category followed by smiling was reliably conditioned, reversed, and reconditioned. For the second mother, that interactive behavior was reliably conditioned, reversed, reconditioned, reversed again, reconditioned again, reversed again, and reconditioned again. These results attest to the efficacy of contingent vocal responses that these mothers assumed to be their own infant's in increasing in each mother the incidence of the two-stage social response of a vocalization followed by a smile. That is, in an interactive context like that which characterizes mother-infant interaction in life settings, mothers' verbal and smile behaviors were conditioned by what they took to be responsive vocal behaviors of their own infants. Interview probes after sessions and the mothers' spontaneous remarks about their infants' performances indicated that these changes in response patterns occurred without the mothers being at all aware of their infants' behaviors being simulated, or of the controlling contingencies operating.

Average Evoked Response (AER), Attention and Perception

The study of attention has been approached by using neurophysiological techniques. A number of investigators have reported that average evoked response (AER) amplitude increases when subjects focus their attention on the evoking stimulus. However, an amplitude increase can result from changes in arousal, stimulus novelty and other factors. By presenting dim and bright light flashes to the left and right hemiretinal fields and recording bilaterally from occipital and temperopreoccipital leads we hoped to find

localized indications of attention. Attentional amplitude increases were two to four times as great for right visual field stimuli--left temperopreoccipital cortex AER as for any other route of stimulation. These results suggest the importance of the left temperopreoccipital cortex for attentional processes and for AER studies in patients with schizophrenia.

Individual differences in the amount of AER amplitude change with attentional deployment are prominent even in normal individuals. Based on relationships between peripheral vascular resistance, sensory intake bahavior and catecholamine levels, we hypothesized that dopamine-B-hydroxylase (DBH) might be a predictor of these differences. In two studies, DBH levels correlated significantly with the amount of amplitude increase in AER when subjects counted stimuli as opposed to doing mental arithmetic. In a third study, uninstructed subjects' AER amplitude correlated highly with DBH. This is intriguing in view of the finding that schizophrenics, often exhibiting attentional deficits, have also been implicated as having low brain DBH.

Effects of and on time perception have been implicated in biological processes from metabolic rate and physiological arousal to cognitive disorientation and variations in mood and emotion. A basic difficulty in identifying the causal relationships involved lies in the fact that variations in fundamental biological processes are often accompanied by emotional and motivational changes, and it is not certain whether discriminative capacity or attitudinal disposition is affected in any given instance.

We have sought to differentiate between the functional and verbal uses of time and to develop a model of the perceptual process in terms of which the rate of passage of subjective time may be differentiated from constant errors of response in judgments of time. The model is basically that of a linear "internal clock" in which rate is reflected in the slope of the response x time function, and systematic errors of measurement are reflected in the intercept of the function.

We have been able to construct such a model which appears to account for the kinds of variability found in judgments of time intervals. A classic problem, for example, has been that individuals overestimate shorter intervals and underestimate longer ones, resulting in a given intermediate interval of time which is judged with absolute accuracy. This point of absolute accuracy shifts under varying conditions and has been taken as an important indicator of biological functioning. The shifts are not systematically related to other aspects of timing performance nor to appropriate changes in physiological or psychological state, thus resulting in a dilemma of interpretation. In the present model the particular point of absolute accuracy arises from the systematic and random errors of the stystem and is essentially an artifact. In terms of rate, an individual in a given physiological state judges all time intervals accurately or underestimates or overestimates all of them consistently. Also, the rates for different methods of obtaining the judgments agree well with each other.

We have investigated changes in rate as a function of reduced arousal during sleep. Subjects were awakened and tested briefly at intervals during the night. The subjective time rate systematically decreases and then

returns to normal. We have determined that this change is not brought about by practice in the task or by lessened motivation or impaired ability on the part of the subjects. It is also not simply a function of body temperature or of stage of sleep as gauged by present EEG methods. It seems rather to be a change in mental functioning associated with reduced arousal, whether the reduced arousal is brought about by sleep or not. This matter is being investigated further in connection with drug-induced states.

Problem Solving.

We continue to investigate mental processes that are responsible for resolving the enigmatic situations that an individual encounters in his daily transactions with a frequently puzzling environment. Our research is based on experiments in which people conduct inquiries by interacting with systems controlled by computer programs. The results are used for three purposes: (1) to assess the methods commonly used by people in searching for solutions to puzzling situations; (2) to evaluate psychological theories that purport to explain this aspect of human behavior; and (3) to develop methods of improving people's ability to cope with the problems of daily life.

During the present year the "rule learning" paradigm of traditional concept formation experiments was added to our collection of computer implemented procedures and an experiment on this type of problem solving is now in progress. Computer controlled instructions for all procedures were also developed so that entire experiments can now be executed as sets of transactions between the subject and a robot without any possibly disturbing intervention by the experimenter. The programs now control the following components of several experiments: (1) application of the research design in the sense of assigning people to groups that are equated at run-time on the basis of preselected criteria; (2) assignment of tasks to each subject according to the design; (3) execution of the test runs; (4) recording of data; (5) printing summary of results for each subject-run; (6) printing of daily reports summarizing the current status of the experiments and its result.

A new method of analyzing the results of concept formation studies has been developed; it permits at least partially separate evaluation of two formerly confounded aspects of heuristic inquiry: the search for relevant information and the interpretation of data at hand. These results also indicate that some heuristic strategies--e.g., "conservative focussing" (change only one variable at a time) rather than being basic and simple, involve cognitive heterogeneities that need to be analyzed before we can identify some of the heuristic difficulties experienced by the man on the street. However, since the performances of all subjects improved with experience, these data also suggest that the problem solving behavior of most people can be improved with adequate training. It is one of our goals to identify what constitutes adequate heuristic training.

The Menstrual Cycle.

A test procedure involving rest, mild auditory stimulation and task performance was given daily to 17 women over the course of at least one complete menstrual cycle and to 7 men over a 4 week period, during one week of which they received daily doses of progesterone. Reliable changes over the

course of the cycle were shown in a number of autonomic variables and in self ratings of mood, preovulatory changes being even more pronounced than premenstrual changes. The study with the men showed that some, but not all, of the changes occurring during the luteal phase could be explained by fluctuations in progesterone and that the influence of estrogen is probably important. The data from the two studies suggest that "premenstrual tension" may be due to rapid changes in metabolic functioning rather than unusually high or low levels of functioning.

Communication.

Research on conversation has taken two forms, naturalistic and experimental. The first finding had been that young children do not participate in the adult pattern of listeners letting speakers know by head nods and brief vocalizations ("M-hm," "Yeah," etc.) that they are keeping up with the speakers' line of thought. Preliminary observations following up on this finding had shown that children, when talking with each other, do not often require such feedback, since their utterances are very brief, and usually concern only the immediate activity being engaged in. A methodological study was begun last year to develop an observational protocol for capturing these various events. That protocol was refined this year, and has been used to collect a large amount of data. Thus far 121 observations have been recorded, and these were made of 37 situations. The protocol includes the following variables: (1) speaker turns (when one speaker stops talking and another begins); (2) length of speech in a turn (determined by the number of rhythmically marked "chunks" of speech called Final Juncture Units, or FJUs); (3) the content of the talk dichotomized as immediate activity *vs.* reference to remote events; (4) the appearance of Listener Responses or LRs (nods, "M-hm," and the like); (5) whether an adult or a child is talking or responding; and (6) whether the situation is an instructional one or not. In addition, a running account of time is noted, along with the composition of the conversational group in terms of size, sex, and age.

Since the first observations indicated that adult-type conversational patterns appear regularly only at adolescence, the more extended observations have been made in the 6th, 7th, and 8th grades in a private school. In a tentative analysis of the first data (comprising some 1,400 speaker turns and 2,500 FJUs), the age differences show up, there are more LRs to teachers than to other children (talk with teachers is more likely to be instructional), and curiously, a sex difference emerges very strongly: boys give substantially more LRs than girls, both to teachers and to other children.

Behavior Genetics.

We have started a series of experiments to study fighting behavior in mouse sublines derived from a single colony, but inbred in Jackson Lab or NIH breeding colonies for a number of years. These sublines have different levels of the adrenal catecholamine synthesizing enzymes TH, DBH and PNMT. Enzyme levels in F_1 hybrids are intermediate. Mechanisms which could account for the differences in enzyme levels and genetic structures consistant with these mechanisms have been suggested.

The sublines also show clear differences in fighting behavior. One of the sublines, Balb/cJ, fought so that they could only be housed with littermates; the other, Balb/cN, was quite passive. The role of this Laboratory was to develop a precise and sensitive measure which would reflect these observations systematically and to apply the measure to genetic hypotheses about the mice. An isolation-induced fighting paradigm was constructed to measure and categorize readiness (latency) to fight. This was confirmed by testing the parental strains. F_1 hybrids appear to be different from either parent.

ANNUAL REPORT OF THE LABORATORY OF SOCIO-ENVIRONMENTAL STUDIES

National Institute of Mental Health

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Melvin L. Kohn, Chief

Social and behavioral research tends to have a long time-span, a single study often requiring one or two years for designing the study and developing the research instruments, another year or so for carrying out the field work, and as many as six or eight years for data-analysis and interpretation. Thus, in any given year, our studies will be at quite different stages of the research process. On some--those that represent new departures and, at the other extreme, those that are far along into the analysis of already-collected and processed data--there is much that we can discuss in an annual report. On others--those now concentrating on field work or on coding data and preparing them for systematic analysis--there is little to be said other than that this essential part of the work is being done. The vignettes that follow reflect studies at all stages of the research process.

DEVELOPMENT OF SELF-CONCEPTION IN CHILDREN

Morris Rosenberg's research on the development of self-conception in children is well along in data-analysis, as reflected in the last several annual reports. In the past year, analyses have centered on two themes: social context and group disidentification. For both sets of analyses, the primary data are from the survey of school children that Rosenberg and Roberta Simmons conducted in Baltimore, Maryland, in the spring of 1968.

Social Context

The analysis of social context focuses on the consonance or dissonance of the child's immediate social environment, that is, the concordance or discrepancy between the child's own characteristics and those of the people with whom he interacts. In this view, the environment is not in itself consonant or dissonant; it is only consonant or dissonant for a given individual with reference to a particular characteristic. Rosenberg's analysis deals with three types of social context, which he calls identity context, competence context, and values context.

(1) Identity contexts--An individual's social identity consists of the groups, statuses, or social categories by which he is socially recognized and classified in the society: religion, race, sex, national origin, age, and social class. Rosenberg found that dissonance between the child's own religious background and that of the majority of his schoolmates is associated with lower self-esteem and higher rates of psychophysiological indicators of anxiety. Thus, Jewish children raised in predominantly gentile neighborhoods were found to have somewhat lower self-esteem and more psychosomatic evidence of anxiety than Jewish children raised in

Jewish neighborhoods. Similarly, Protestants raised in Catholic or Jewish neighborhoods have somewhat lower self-regard than those raised in neighborhoods inhabited chiefly by co-religionists. And the same holds true for Catholics. In general, the relationship between the religious background of an individual and those of the people in his immediate environment have an important bearing upon his feeling of self-worth.

Examination of the racial context yielded similar results. Black children in predominantly white schools have lower self-esteem than black children in predominantly black schools. In part, this results from the direct racial discrimination experienced by those in predominantly white schools.

Social class dissonance has been difficult to study because economic segregation is widespread and is further contaminated by racial segregation. Nevertheless, it is possible to classify the socioeconomic status of the child and the mean socio-economic level of his school. The data show that both black and white children whose socio-economic level is below that of their schools tend to have somewhat lower self-esteem; among white children, those whose SES is above average also have lower than average self-esteem, but this pattern is ambiguous for comparable black children.

Religion, race, and class are, of course, socially ranked elements of identity. Whether similar effects would appear with regard to social categories that are not hierarchically ranked, or in environments in which minority group members fulfill some special social function, remains to be learned.

(2) Competence contexts--In addition to the group memberships and social statuses that characterize any individual, he also has a multiplicity of personal characteristics and achievements. The consonance or dissonance between these characteristics and those of his immediate social environment can also be pertinent for self-esteem. In the Baltimore study, for example, it was found that black pupils with "borderline" grades who are attending predominantly black schools where the average grades are relatively high have lower self-esteem than those in schools where the average level of performance is closer to their own.

(3) Values contexts--Here consonance is reflected not in the concordance of individual and environmental characteristics, but in the relationship of the individual characteristic to what is valued in his environment. In high schools where athletic ability is valued, for example, boys designated as "best athlete" appear to have higher self-esteem than boys of equal athletic skill in schools where this quality is less regarded.

The data thus indicate that identity contexts, competence contexts, and values contexts may all affect the individual's self-esteem. There is some evidence to suggest that these social contexts may also affect the stability of the self-concept. Thus, with level of self-esteem statistically controlled, black children in dissonant racial contexts are found to be conspicuously more likely than those in consonant contexts to have unstable

self-concepts. With regard to religious dissonance (again with level of self-esteem statistically controlled), no association between contextual dissonance and instability appears for Jews, but some association does appear for Protestants, and a definite relationship is found for Catholics. While it is not entirely clear how contextual dissonance exercises these effects, there is reason to think that the attitudes of members of the majority group toward the individual may not correspond with his own: in failing to provide interpersonal confirmation of his self-hypothesis, these reflected appraisals are likely to give rise to uncertainty and instability in his self-image.

That the social environment is an important factor in personality development and social behavior is both a matter of immediate experience and an established dictum of social psychology. Yet the same social environment will affect different people differently. One reason, this research suggests, is that this environment may be consonant for some, dissonant for others. Rosenberg's research has sought to specify how different contexts may affect different aspects of the self-concept.

Group Disidentification

That the individual's membership and reference groups may constitute important components of his self-concept has long been recognized in social psychology. It is thus understandable that writers on problems of minority groups have used such expressions as "self-hatred among Jews" and "black self-hatred" to describe the plight of minority group members who internalize the negative majority attitudes toward themselves. What such discussions overlook, however, is that attitudes toward one's group and attitudes toward oneself may be entirely different. Rosenberg's analysis has therefore attempted to examine the question: Does group disidentification lead to low self-esteem?

In this study, group identification was examined in terms of the child's desire to be a member of his own or some other ethnic group, pride in the group, importance of the group, and inseparability of group and self. The results show virtually no relationship between group identification and individual self-esteem. Thus, the self-esteem of black children who did not identify with blacks is just as high as that of black children who identify strongly. Religious group identification yielded essentially similar results.

Further analysis was undertaken to account for this unexpected empirical finding. To do this, Rosenberg attempted to determine how much the child identifies with 16 possible "ego-extensions" (e.g., mother, father, family, siblings, race, religion, clothes, school work, friends, father's job, school). The results show that while race and religion are widely felt to be an integral part of the self, mother, father, and siblings are even more important extensions of the child's ego, and other things, including clothes, friends, father's job, and school, are also chosen by more than half the sample. What writers on minority groups consider of prime, if not exclusive, importance must in reality take its place alongside many others important to the individual in forming his general self-assessment.

What holds true for group memberships obtains equally with regard to personal attributes. There are many personal attributes that may arouse pride or shame in the individual and which may be experienced as more central to the self than one's racial or religious group. One way to judge this matter is to see whether the individual's pride or shame in his own characteristics (intelligence, appearance, social skill) are more closely related to his global self-esteem than are certain aspects of social identity (race or religion). The data show that the correlations between the individual's own characteristics and his self-esteem are much stronger than the correlations between group memberships and self-esteem. Furthermore, those children who are proud of their own characteristics but not of their groups have higher self-esteem than those who are proud of their groups but not of their own characteristics.

It is frequently overlooked that race and religion are ascribed statuses, i.e., assigned the child at birth, and have nothing to do with the individual's own achievement. Feelings of pride or shame in such statuses turn out to have less bearing upon the individual's feeling of self-worth than statuses for which he himself is responsible: the data show that the relationship between group pride and self-esteem is much weaker than the relationship between school grades or social success and self-esteem.

Whether the individual is proud or not proud of his racial or religious group, then, has little bearing upon his global feeling of self-worth. While the individual's race and religion are important, they are only two of a large number of elements that enter into self-esteem formation; nor are they necessarily experienced as central to the self. In those cases in which these groups <u>are</u> felt as integral to the self, however, the data show that lack of pride in them <u>does</u> lower self-esteem.

STUDIES OF YOUNG CHILDREN'S SOCIAL SENSITIVITIES

For this program of research--conducted by Marian Yarrow, Carolyn Waxler, and Robert King--this has been a year of field work. Last year's annual report described the two major studies they are presently conducting. One is designed to document the growth and early development of the very young child's ability to comprehend and respond to other people's feelings and emotional states; this study is being conducted in the natural setting of the home environment. The other project, an experimental study of the development of altruism in young children, is being conducted in a nursery school. In both studies, fieldwork has been intensively carried out throughout the year. Next year the shift will be to equally intensive data-analysis.

RESEARCH ON THE INTERNALIZATION OF RULES, STANDARDS AND VALUES

Roger Burton's current work in this area centers on designing a new experimental study of cognitive factors in children's development of moral standards. Previous studies have shown that although honesty is largely situationally determined, there is a modest generalized tendency for

individuals to react consistently in a variety of experimental situations. There is evidence, too, that consistency of behavior varies among individuals. Thus, some persons are unpredictable from one situation to another, whereas others are consistently honest or deceitful.

To account for these individual differences in consistency, it has been proposed that two facets of learning are involved in behavior elicited during situations in which the individual is presumably tempted to be dishonest and that these determine the extent to which there is transfer (or generalization) from situation to situation. The first facet encompasses factors limited essentially to the immediate external physical situation, for example, whether the person is alone or others are present and the locus of the situation (whether home, school, or playground). The second facet involves the way the person conceptually classifies the situation. When a child learns that a particular response is appropriate to a specific situation, he may also learn that this situation is an instance of a more general concept, honesty. This research is now exploring how behavior learned for a specific situation might be linked to the concept of honesty in such a way that subsequent behavior in distinctly different situations becomes more consistently honest.

Extensive pretesting has established the plausibility of the model and has validated the particular tests to be used in the study proper.

HEALTH ORIENTATIONS OF CHILDREN

The central issue in John Campbell's research is to ascertain how children acquire and modify their perspectives on illness and health. The study is based on focused interviews and questionnaires provided by a sample of 264 hospitalized children and their mothers, as well as ratings of the children's behavior by attending nurses.

Evidence summarized in past annual reports indicated that children directly adopt their parents' definitions of illness to only a very limited extent, although some parent-to-child transmission does appear to be the case for the more value-laden area of standards of appropriate behavior in health-relevant circumstances. Additional analyses show that much of the child's own perspective on health-relevant issues can be viewed as determined by the cumulative impact of (a) the child's own status, (b) the general circumstances of his family, and (c) status-related parental values. The role of these factors is clearly evident in children's assessments of their health-relevant risk taking, their behavior when ill, and their own <u>standards</u> for appropriate behavior in such health-relevant circumstances.

Ascription of status on the basis of age and sex, as Linton long ago pointed out, is common to all societies. At a relatively early age children learn that such status ascription also implies concomitant culturally prescribed standards for behavior. Although the person who is defined as ill may be relieved of certain conventional role obligations, sick-role functioning, nevertheless, exacts its own requirements of the patient. And the nature of such functioning is very much related to

age- and sex-typing. Indeed there is a considerable parallel between age and sex in terms of their impact on children's health orientations. Spartan standards for emotional expression when faced with the stressors of illness are characteristic of older children and boys, who say they should display relatively little emotion in such circumstances and characterize their own actions as conforming to these norms. Older children and boys are also more inclined than younger children or girls to reject the sick role (as indicated by a scale measuring preference to keep active, rather than to give in to illness, disinclination to see the doctor, shrugging off minor injuries, and a tendency to curtail the duration of convalescence). In risk-taking behavior, boys and older children also show similarity. They, in contrast to girls or younger children, see themselves as more apt to take risks that might conceivably lead to illness or injury.

An additional powerful predictor of children's health orientations is family socioeconomic status. This probably helps shape children's perspectives on health and illness in an indirect fashion; the social circumstances of the family have a sizeable influence on parents' general childrearing values, and these in turn help determine the climate in which children acquire their health orientations. The data of this study confirm that a family's position within the social structure is linked to parental valuation of self-direction in the child: the higher a family's socioeconomic status, the greater the likelihood that the parents will attach importance to self-direction. These data also show that socioeconomic status and parental valuation of self-direction make generally independent and parallel contributions to children's health orientations. The higher the social status level or the greater the mother's valuation of self-direction, the more likely are the children to reject the sick role, to minimize the extent of their emotional reaction to illness, and to be more casual about taking risks that might lead to illness or injury.

Each of the four status-relevant variables considered (age and sex of child, socioeconomic status of family, and status-linked parental valuation of self-direction) makes an appreciable independent contribution to children's health orientations. Multiple-regression analyses confirm that their combined effects are considerable: The average multiple-correlation coefficient between these four variables and the several dimensions of health orientation here considered is greater than 0.30; the largest is nearly 0.60. Thus, it appears that the cumulative impact of status-linked cultural prescriptions for role functioning is at least as much in evidence in children's perspectives on health and illness as it is in more general social orientations.

THE SOCIAL-STRUCTURAL ORIGINS OF STRESS

Leonard Pearlin's inquiry into the social-structural origins of stress is now at the point where the data have been collected and processed and systematic analysis has begun. The main thrust of the inquiry is to trace the influence of social structure--especially race, class, sex, and age--on people's exposure to potentially stressful situations, their subjectively experiencing these situations as stressful or nonstressful,

their modes of coping with stressful situations, and the longer-term consequences of these experiences. The data are based on a survey of 2300 households in the Chicago urbanized area.

The long-range goal of this study is a systematic cross-institutional analysis, examining stress as it occurs and is dealt with in occupational, family, economic, and other major institutional spheres. Although data-analysis is proceeding on all these fronts, most of the findings are too preliminary to report at this time. One small part of the analysis that is far enough along to report concerns stresses attendant on status discrepancies in marriage. In marriages between people of unequal status, the person of the higher status origins is relatively likely to experience difficulties in several crucial areas, including the ability to communicate meaningfully with his spouse, to give and to receive affection, and to share important values. The mate who bears the higher status is also disposed to feel that in the over-all give and take of his marriage, he emerges at the losing end of the exchange. By contrast, people who have married up are least likely to experience these strains. Where such strains do exist in marriage, they are likely to be closely associated with subjectively-experienced stress. Thus, the way that social statuses are combined in a marriage affects key elements in marital relations; where these elements are disrupted, emotional stress is likely to ensue.

PARENTAL CARE AND CHILD BEHAVIOR IN JAPAN AND THE UNITED STATES

Since William Caudill's death in 1972, Carmi Schooler has been working at completing the analysis of the rich body of comparative data Caudill had collected. Caudill had conducted a longitudinal observational study of the behavior of parents and children over the first six years of life in Japan and the United States. During 1961-64, 30 Japanese and 30 American middle-class mother-infant pairs were selected for observation. The infants were first-born, normal babies, and were three-to-four months of age at the time of observation. The first 20 Japanese and the first 20 American cases were again observed when the children were 2-1/2 years of age, the observations in the home being completed during 1963-1967. These same children were studied for a third and final time at 6 years of age during 1967-70; all observations were completed before Caudill's death.

Caudill's own analyses were limited to the data of the earliest time period, when the children were three-to-four months old. He found that there was a sharp difference in the maternal practices of the Japanese and American mothers. American mothers tend to view their babies, at least potentially, as separate and autonomous beings who should learn to do and to think for themselves. Even the period of infancy is characterized by an emphasis on the psychological separateness of mother and infant, and the development of relatively sharp ego boundaries between the two. Thus, American mothers de-emphasize the importance of physical contact, such as carrying and rocking, and verbally encourage their infants to explore, and learn to deal with, their environment by themselves. American mothers are more encouraging of their babies to reach out for toys and to be physically active. And just as American mothers think of their infants

as separate individuals, so also do they think of themselves as separate persons with their own needs and desires, which include time apart from the baby to pursue their own interests and to be wives as well as mothers.

In Japan, in contrast to America, mothers view their babies much more as extensions of themselves; the psychological boundaries between mother and child are blurred. Japanese mothers place less importance on vocal communication and more on physical contact; and the expectation is that mothers will devote themselves to their children without any great concern for a time away from the child, even for a separate time to be with one's husband. This expectation extends to the custom of parents and children sleeping together in the same room.

A comparison of the data on infant behavior in the two cultures shows a basic similarity in the biologically rooted behavior of the infants, for example in the total time spent sleeping or eating. Beyond these essential similarities, however, there are distinct cultural differences: American infants show greater amounts of gross bodily activity, play (with toys, hands and other objects), and happy vocalization; in contrast, Japanese infants seem more passive, their only arena of greater activity being in the amount of unhappy vocalization. Thus, even at three-to-four months of age, there are sharp cultural differences in the behavior of the children--differences entirely consonant with those in their mothers' child-rearing practices. The implication is that culturally patterned differences in child-rearing practices make for culturally patterned differences in child behavior.

Schooler's analyses have attempted to determine whether these cultural differences in maternal practices and child behavior extend beyond infancy to the two later time-periods at which Caudill observed these mothers and children. His analyses indicate that the essential cross-cultural differences in behavior found when the subjects were infants are repeated at age 2-1/2 and again at age 6. Compared to Japanese mothers, Americans are likely to be more physically active, more vocal, more affectionate, and more likely to discipline their children, while Japanese mothers are more likely than are Americans to encourage dependent behavior in their children. Compared to Japanese children, Americans are more active, more vocally and physically emotional, more independent, and more likely to manipulate functionally both their social and physical environments. Thus, at each of the childhood periods, the cross-cultural differences in the behavior of mothers and children seem to mirror each other, the children's behaviors seeming to be the logical outcome of the culturally different patterns of parent-child interaction at infancy. From these results, it seems likely that a considerable amount of culturally patterned behavior has already come into being by 3 to 4 months of age and is re-inforced as the children grow older.

Some caution is needed in generalizing from these findings. The sample consists of individuals born at a given time (1961-1964), into a given social class (middle), and in two specific countries (Japan and the United States). It is possible that results would have been different if the subjects from the two countries had been born at another time, or

into a different social class. An even greater limitation is that we are comparing only two cultures; thus, to say that Japanese children are less verbal or less independent than American children does not imply that they are non-verbal or dependent in any absolute sense. In fact, at age 6 Japanese children show verbal behavior in 60 percent of the observations. It is quite possible that, if Japanese or American children had been compared to children in some other culture, the tenor of these findings would be different. Nonetheless, Schooler's analyses make it even more clear that Caudill's work was an important step in demonstrating the early and persistent effects of culture on personality.

OCCUPATIONAL EXPERIENCE AND PSYCHOLOGICAL FUNCTIONING

The major accomplishment of Melvin Kohn and Carmi Schooler's work on the social psychology of occupations this year has been the planning and development of a follow-up survey, designed for reinterviewing a subsample of 750 of the men interviewed ten years ago and, this time, their wives and in some families a child as well. Since the follow-up study represents a major new phase in a continuing research program, it is appropriate to review the earlier phases of the research and the rationale for the new survey.

The research began in 1957 with a study in Washington, D. C., addressed to confirming earlier reports about class differences in parents' child-rearing practices and to discovering whether these differences in parental practices could be traced to class differences in what parents value for their children. It was found that social class position is significantly related to both fathers' and mothers' values for their children, with parents of higher social class position valuing self-direction more highly, and parents of lower social class position valuing conformity to external authority. Moreover, these class differences in parental values have important consequences for their child-rearing practices, both for disciplinary practices and for the division of responsibility, between mother and father, for providing support and for imposing constraints on the children.

A second study, conducted by Leonard Pearlin in 1963 in Turin, Italy, showed that social class position has essentially the same effects on parental values in the very different historical, cultural, and economic circumstances of Italy and the United States. This study also indicated that class differences in fathers' values (and to a lesser but still substantial degree, in their wives' values) could be interpreted largely in terms of class-related differences in men's occupational conditions, particularly those involved in the exercise of self-direction in work--notably closeness of supervision, routinization, and the substantive complexity of the work.

A third study--this one a survey in 1964 of a cross-section of all men employed in civilian occupations throughout the United States--made it possible to extend these findings in several important respects. First, these data demonstrated a remarkable generality to the relationship between

class and paternal values: the relationship exists and is of approximately equal strength in all segments of American society. Second, these data show social class to be more strongly related to paternal values than is any other major line of social demarcation, more strongly in fact than all other major lines of social demarcation combined. Third, the importance of occupational conditions for explaining the relationship between social class and paternal values is much more firmly established by these data than by those from Turin. And finally, these data show that class and occupation are related not only to parents' values for their children, but also and in exactly the same way to their values for themselves, to their self-conceptions, and to their social orientations.

These findings establish a prima facie case that men's social class position affects their values and orientation, at least in substantial part, because of class-related conditions in their occupational lives. But this explanation assumes that the interrelationship of class, occupation, and values is not just a function of what types of men go into what types of jobs, and of men's efforts to mold their jobs to fit their needs and values. In further analysis, borrowing from the analytic techniques of the econometricians, it has been possible to show that the effects are not all one way: that the job does affect the man; the analysis suggests, in fact, that the effects of job on man are stronger than are the reciprocal effects of selective recruitment and job-molding.

But even the application of econometric techniques to the analysis of the reciprocal effects of job on man and man on job cannot definitively show change in particular individuals. Nor does it provide much information about the learning mechanisms involved in transferring the lessons of the job to nonoccupational realms of life. To accomplish these goals requires a follow-up study of a substantial subgroup of the sample, inventorying their current job conditions, recording all changes in their occupational conditions since the survey was conducted in 1964, and re-measuring all the principal facets of psychological functioning examined in the earlier study. This is the study now being carried out.

Another objective of the follow-up study is to interview the wives of all those men who are currently married, using interview procedures closely parallel to those used in the interviews with the men. There are three principal reasons for interviewing the wives.

One reason is to fill in a major gap in the work thus far: since the 1964 survey was limited to men, the analyses to date tell us nothing about the effects of occupational conditions on the psychological functioning of women. Admittedly, the sample of wives is not optimum for this purpose, not only because no sample of wives will be representative of all women, but also because the wives in this sample are all married to men who are between the ages of 26 and 65. Nevertheless, if these sample biases are kept firmly in mind in analyzing and interpreting the data, much can be learned from such an inquiry.

A second reason for interviewing the wives is to examine the relationship between men's occupational conditions and their wives' psychological

functioning, as well as that between the wives' occupational conditions and their husbands' psychological functioning. The Turin study showed that men's occupational conditions are meaningfully and apparently causally related to their wives' values. But this research gave no information about the processes involved, nor did it examine the corresponding effects of wives' occupational experiences on men's values and psychological functioning. Parallel interviews with husbands and wives should enable us to do both.

The third reason for interviewing wives is to study the processes of "value-transmission" from parents to children. Such an analysis requires information from both parents, with respect to both parents' experiences, both parents' values, and both parents' perceptions of family relationships.

For all these purposes, we need data on the wives' occupational experiences. A major problem here, of course, is that many wives do not have jobs outside the home. But most "unemployed" wives do a substantial amount of household work, and some work in volunteer activities. We are trying to assess these activities in the same terms as paid jobs, by treating household work and volunteer work as "occupations," to be studied in much the same way as other occupations. (We are treating men's household and volunteer work in exactly the same way.)

Still another objective of the follow-up study is a survey of the children of some of the men interviewed in 1964. In the 1964 survey, all questions about parental values and child-rearing practices were asked with reference to one specified child, who had been randomly selected by procedures designed to give an approximately equal distribution of boys and girls at every age level from 3 through 15. This specific child is to be the subject of the children's part of the present inquiry. Thus, the age range of the children, ten years later, will be 13 through 25. Our intent is to try to interview these children wherever they now live, wherever they may be in their educational, occupational, and family careers.

The earlier studies provide evidence for a causal chain of considerable importance in understanding the personality development of children: from parents' social class position and attendant occupational experiences to parental values to parental practices. What is lacking is the next and crucial link in this causal chain: from parental values and child-rearing practices to the psychological development of the child. The data on paternal values and childrearing practices collected ten years ago, together with the data now to be collected from a subsample of these fathers and their wives, provides an excellent opportunity to study this crucial link in the causal chain. The critical interpretive problems in past studies of what has come to be called "the transmission of values in the family" has been the lack of relevant time-series data. The planned study of the children should enable us to deal with this problem directly.

Two new sets of questions have been developed for the children's study. One concerns parent-child relationships and identification with the parents. The primary intent here is to develop indices that can be

used as intervening variables, in explicating the processes by which parental experience influences children's values and psychological functioning. That is, we hypothesize that the effect of father's experience and values on child's values will be mediated by the nature of the father-child relationship and by the degree of identification of child with father; similarly for the mother-child relationship.

The other new element in the inquiry with the children is a set of questions about their educational experiences, to be asked of all children who are still in school. Since the amount of interview time available is too limited for us to explore all facets of the educational experience, we chose to concentrate on those that parallel the main dimensions of occupational experience: the degree of self-direction and of intellectual flexibility permitted and encouraged by the school experience.

At the time this report was written, interviewing of the main sample of men, wives, and children had just begun.

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Two senior members of the Laboratory, Morris Rosenberg and Roger Burton, have accepted professorial appointments at the State University of New York at Buffalo. Their leaving ends a long era of remarkable stability in the Laboratory's senior personnel. Both men have contributed greatly to our research and to the intellectual life of the Laboratory; they will be missed.

Annual Report for 1974

Laboratory of Brain Evolution and Behavior

National Institute of Mental Health

Paul D. MacLean, M.D., Chief

Human communicative behavior can be broadly characterized as verbal and non-verbal. It is non-verbal behavior that we possess in common with animals. It has been the special contribution of ethology to provide the first systematic insights into animal communicative behavior and to show that, like verbal behavior, it has its semantics and syntax -- in other words its meaning and orderly arrangement of specific acts. One of the major purposes of this Laboratory is to investigate forebrain mechanisms underlying communicative behavior of animals.

Since animal experimentation provides us our only systematic knowledge of brain functions, it is necessary to say a few words about the justification of using findings on animals for drawing inferences about the workings of the human brain. At the molecular and cellular levels, discoveries in animals are readily acknowledged as applicable to human biology. Neurochemical and neuropharmacological studies in animals, for example, have helped to revolutionize the treatment of certain forms of mental illness. Somewhat ironically, however, many people believe that investigations on brain mechanisms of animal behavior have little human relevance. Such attitudes perhaps stem from a failure to realize that in its evolution the human brain expands along the lines of three basic formations that may be characterized both anatomically and biochemically as reptilian, paleomammalian, and neomammalian.

The Section on Comparative Neurophysiology and Behavior has focused particularly on the role of the two older evolutionary formations of the brain in animal communicative behavior. Experiments conducted during the past year further delineated pathways of the reptilian type brain (striatal complex) and of the paleomammalian type brain (limbic system) that are essential for the expression of genetically constituted, species-typical behavior. Judged clinically in the light of various case material, the findings would indicate that the pathways to and from the two older evolutionary formations of the brain are essential for those forms of non-verbal behavior that are expressive of the basic personality.

The Section's work on the anatomy and functions of exteroceptive and interoceptive inputs to phylogenetically ancient parts of the forebrain has continued. Recent studies by

H. Montager in France, which have demonstrated the important role of olfaction in mother-child relationships, underline the need for further knowledge of olfactory mechanisms. With the use of a refined apparatus for testing olfactory discrimination in rats, it was found that there is significant sparing of olfactory function following interruption of the main olfactory pathway or destruction of large areas to which it projects. Behavioral and anatomical studies of the past year have provided firm evidence that heretofore dubious projections from the ipsilateral limb of the anterior commissure to the olfactory tubercle and hippocampal rudiment may account for sparing of olfactory function under the above conditions.

In view of the prominence of visceral symptoms in certain forms of mental and other illnesses, it is curious that so little is known about the influence of interoceptive systems on cerebral function. The vagus nerve conducts impulses to the brain from the heart, lungs, stomach, and other viscera. In awake, sitting squirrel monkeys it was found that vagal stimuli elicited responses of cells in intralaminar nuclei and neighboring structures. Particularly noteworthy was a large percentage of responsive cells (with response latencies as short as 12 msec) in the paracentral nucleus. This nucleus has long been recognized as part of the diffuse thalamic projection system, but nothing specific has been known about its functions. Since it projects to the cingulate and other midline cortex, the results help to explain the findings of a companion study that vagal volleys activate units in these cortical areas.

Other activities of the Section include ethological observations on reptiles preparatory to studies on forebrain mechanisms of species-typical behavior and exploratory work on dogs regarding the role of the striatal complex in breed-typical behavior. Finally, an atlas has been prepared of the brain of the albino mouse which, upon publication, will extend the use of this valuable experimental animal in neurological and behavioral research.

The Section on Comparative Biopsychology has obtained significant additional information about the effects of neonatal experience of dogs on their later development. Earlier work of the Section had shown that puppies removed from the dam at one week were subsequently slower in initiating responses in the learning situation than animals removed at 2 weeks. These findings have been replicated, and in addition, it has been found that the animals removed earlier from the dam were slower as adults in initiating responses in the learning situation. Once started, however, they learned as rapidly as the other animals. It was possible that the lag in initiating behavior was attributable to the experience in the early learning situation or correlated factors. Further experimentation has shown,

however, that hand-fed puppies separated from the dam and subjected to no testing are slower as adults in initiating responses in a learning situation. One possible explanation is that animals separated from the mother gain less weight and because of their lesser size are dominated by their littermates. Other factors must be considered, however, since nutritional factors may affect brain development, as well as gross bodily size.

With the acquisition during the past year of large outdoor enclosures for rearing whole litters, the Section will be able to have a broader base for its longitudinal ontogenetic studies and, apart from experimental observations within the laboratory, obtain ethological measures of an animal's freely expressed behavior.

The Section on Behavioral Systems has continued the analysis of its studies begun in 1966 on the effects of overpopulation in colonies of mice. A significant finding has emerged from the further analysis of the experiments concerned with "social velocity," a term referring to a measure of an animal's social interactions and mobility. It has been found that when a group reaches a size that is twice the optimum, it divides into two subgroups. One subgroup shows the expected spread in velocity ratings, whereas the velocity measurements for the other group are so low as to make it impossible to distinguish between individuals. It was as though a new behavioral type had precipitated out from the same genetic strain of mice.

In anticipation of future studies, further progress has been made on designing an experimental habitat in which a computerized system affords a continuous record of the location and direction of travel of all members of the group or subgroups, and at the same time affords the programming of certain activities (e.g., cooperative drinking). Such environmental habitats for the study of "social physics" will add to the information formerly derived by visual observation alone.

In cooperation with the National Library of Medicine, the Section devised a novel matrix-search strategy for obtaining a cross-indexed list of references dealing with psychosocial consequences of "population and environment." The bibliography includes more than two thousand references. It was significant that in terms of numbers of papers, there was a great number concerned with the effects of isolation and deprivation, but relatively few dealing with the consequences of social living within a culturally enriched environment. It is a tribute to the work of the Section that Dr. Calhoun was invited to be a participant in the recent London Times - United Nations Conference on "Exploding Cities."

Annual Report of the Laboratory of Cerebral Metabolism
National Institute of Mental Health
Louis Sokoloff, Chief
July 1, 1973 through June 30, 1974

Each of the three Sections of the Laboratory of Cerebral Metabolism has continued its investigations in the same programs which they have been pursuing over the past several years. Restricted resources particularly with regard to positions have precluded any major new initiatives, but fortunately the existing projects are sufficiently fundamental and broad in their implications that they remain contemporary, relevant, and significant in the light of current developments. The research of the Laboratory has been very substantially facilitated by the availability of guest workers who choose to work in the Laboratory because of the nature of its research projects although they are supported by other agencies or organizations.

Section on Developmental Neurochemistry
Louis Sokoloff, Chief

This Section has continued investigations in its four major areas of interest: a) the biochemistry of postnatal maturation of the mammalian brain; b) the mechanism of action of thyroid hormones and the biochemical basis of their role in postnatal development; c) the biochemical mechanisms of the alcohol-withdrawal syndrome; and d) the circulation and energy metabolism of the brain in various physiological, pharmacological, and pathological states.

Studies by Dr. Michael J. Schmidt and Mr. J. D. Brown were pursued on the role of the cyclic AMP system in the regulation of protein synthesis in the developing brain. Protein synthesis in brain is high shortly after birth and then progressively declines eventually to one-fourth that level in adult life. This pattern of change is almost reciprocally related to the development of the cyclic AMP system in brain. Studies in this project have demonstrated that microsomes contain cyclic AMP-dependent protein kinases and that ribosomal proteins, on which the final stages of protein assembly occur, are suitable substrates for the protein kinases. These studies have been completed. The second part of these studies, namely, the determination of how much influence phosphorylation of ribosomal proteins has on the rate of protein synthesis, is still in progress. Preliminary results

indicate that the influence on the overall rate of protein synthesis is probably small, but the possibility that cAMP-dependent phosphorylation of ribosomal proteins may influence the synthesis of specific proteins remains to be determined.

Previous studies in this project demonstrated that thyroid hormones stimulate protein synthesis, and studies have been continued to identify the biochemical mechanism of this effect. The effect on protein synthesis has been found to be secondary to an earlier energy-dependent reaction between thyroxine and mitochondria which leads to a small, stable molecule responsible for the stimulation of protein synthesis. Studies designed to identify this intermediate were interrupted to examine the claim made by another laboratory that the stimulation of protein synthesis can occur without the involvement of mitochondria. These studies have established and identified an artifact in the studies of this other laboratory arising from their injudicious use of uniformly labeled radioactive amino acids of very high specific activity. Such compounds are generally contaminated with other radioactive compounds. These results which are in the process of being published are a timely reminder of the need for caution in the interpretation of results of studies with radioisotopes. The project is now being redirected back to the studies on the nature of the biochemical reaction between the thyroid hormones and the mitochondria and the identity of the intermediate responsible for the stimulation of protein synthesis. These studies are being carried out by Dr. Elaine E. Kaufman and Miss Patricia A. Roberts. These studies also include critical comparisons between mitochondria of immature brain and of mature brain and liver. Earlier studies in this project established that the loss of thyroxine-sensitivity in brain after maturation was due to a change in mitochondrial function. This change is accompanied by a failure of mature brain to respond to thyroid hormones with an increased metabolic rate or with an increased rate of protein synthesis. The system used in the current studies provides an opportunity to identify the nature of the change in brain mitochondrial function.

In the course of the studies of the effects of thyroid hormones on protein synthesis, it was observed that thyroid hormones also influence ion-stimulated ATPases believed to be involved in the transport of monovalent and divalent cations between cells and their environment. The membrane potential of nerve and other types of cells are presumably maintained through the action of some of these ATPases. This effect of thyroid

hormones has been further investigated by Mrs. Barbara A. Jant. She has found that the effect of thyroid hormones is not specific to any single class of ion-dependent ATPases but is exerted indiscriminately on Na^+,K^+-dependent, Ca^{2+}-dependent, and Mg^{2+}-dependent Atpases. In vitro the effect is seen in both brain and liver and is inhibitory in nature. In vivo the effect does not occur in brain, in agreement with the known thyroxine-insensitivity of mature brain, and it is stimulatory in liver rather than inhibitory. The stimulatory effect in vivo is related to the nutritional state of the animal. Indeed, starvation alone stimulates the ATPases just like thyroxine. It is well known that many of the physiological effects of thyroid hormones are closely intertwined with the nutritional state of the organism. This system may serve as a useful laboratory model to study the nature of the relationship as well as to define further the mechanism underlying some of the hormone's diverse cellular effects.

One of the changes in brain mitochondria which occurs with brain development is in their content of the enzyme D(-)-β-hydroxybutyrate dehydrogenase. Previous studies demonstrated that this mitochondrial enzyme is low in brain at birth, rises in infancy during nursing, and then declines again after weaning. These findings contributed significantly to the current awareness that the brain is not necessarily limited to glucose but can and does at certain periods in life utilize ketone bodies as the fuel for its energy metabolism. This utilization of ketone bodies occurs whenever ketosis occurs, as during feeding on ketogenic diets, such as maternal milk, or during starvation. This utilization is made possible mainly by this enzyme and also by others in this metabolic pathway which are all particularly high in brain in infancy. The mechanism of regulation of the enzyme level in brain mitochondria is of particular interest. Drs. R. J. S. Duncan, Glenna G. Fitzgerald, and Elaine E. Kaufman have been working on the solubilization and purification of the enzyme so that antibodies to it can be produced and used to determine whether the changes in enzyme levels reflect changes in enzyme synthesis or stabilization of the enzyme by its substrate. The enzyme is normally a constituent of the inner mitochondrial membrane, and purification of membrane-bound enzymes is itself still a research project in its own right. Nevertheless, the enzyme has been solubilized and partially purified, and it has been learned that the enzyme from brain is fully dependent on the presence of a phospholipid, specifically lecithin. Studies are currently in progress to identify the species of lecithin

involved and the nature of its involvement in the enzyme activity. It is also possible that the changes in the activity of the enzyme in brain with development are reflections not of the amount of apoenzyme but of the level of this apoenzyme co-factor. Studies are planned to investigate this possibility. Recently completed studies have demonstrated that the enzyme is present in both neuronal and glial cell lines.

Studies by Dr. Gilman D. Grave have demonstrated that the changes in brain D-β-hydroxybutyrate dehydrogenase in brain during infancy are influenced by the level of thyroid function. Hyperthyroidism accelerates the pattern of postnatal development. On the other hand, the direct action of thyroid hormones on the enzyme in vitro is a strong inhibitory one. Thyroxine inhibits the dehydrogenase competitively with both its substrate and its NAD^+ coenzyme. At the levels of NAD^+ present in the mitochondria normally, thyroxine would inhibit significantly at concentrations as low as 10^{-9} M, a concentration equivalent to its level in vivo. Hyperthyroidism, as well as hypothyroidism, is known to be injurious to brain development in early postnatal life. These results may indicate the reason. The brain in infancy is dependent on ketone bodies for its energy supply, and inhibition of the dehydrogenase by thyroxine would then limit its energy metabolism.

Studies on the biochemical mechanisms of the alcohol-withdrawal syndrome have been continued in collaboration with Dr. Neil H. Raskin of the University of California, who first began to work on this project while a member of this Laboratory. This project demonstrated the presence of small amounts of alcohol dehydrogenase activity in brain. Recent studies have shown that this enzymatic activity as much as doubles with chronic alcohol ingestion. This rise is slow, not reaching its maximum level in rats for at least 2 weeks following the beginning of alcohol feeding. On the other hand, the enzyme rapidly returns to normal within 48 hours after alcohol-withdrawal. The kinetics of these changes in enzyme activity suggest that the rate of enzyme degradation is decreased by alcohol intake. That the changes in enzyme activity in brain may have functional significance is suggested by the recent findings that the time course of the development of tolerance to alcohol and its extinction following alcohol-withdrawal follow almost the same time course as the changes in enzyme activity.

Studies by Dr. Charles Kennedy, Dr. Michel H. Des Rosiers, and Mrs. Jane W. Jehle, in collaboration with Dr. Clifford S. Patlak and Mrs. Karen D. Pettigrew of the Biometrics Branch, NIMH, and Dr. Martin Reivich, previously of this Laboratory but presently at the University of Pennsylvania, have finally led to the development of a practical and operational method for the quantitative determination of the rates of glucose consumption in the structural and functional components of the brain. The method employs [^{14}C]deoxyglucose as a tracer for glucose metabolism. The method has thus far been used to determine the rates of glucose consumption in as many as 45 structures of the rat brain in the conscious state and during barbiturate anesthesia. The results reveal wide differences in glucose consumption in the various parts of the brain in the conscious state, and anesthesia causes a general reduction in glucose consumption with a narrowing of the differences. The results also demonstrate a very close correlation between local cerebral blood flow and local cerebral metabolic rate, thereby providing evidence that local blood flow is adjusted to local metabolic needs. Studies on the effects of visual stimulation and blinding in rats and monkeys indicate that the method can also be used to map functional neural pathways in the CNS and may be a useful tool in neurophysiological studies. Current plans include studies on the effects of anxiety-provoking drugs such as epinephrine, psychotomimetic drugs, such as LSD, etc. to identify those areas of the brain whose metabolism is most prominently altered in abnormal behavioral states.

Section on Myelin Chemistry
Marian W. Kies, Chief

This Section has continued its studies on the relation between the molecular structure of myelin basic protein and its biological activity in inducing allergic encephalomyelitis (EAE). Sensitization with basic protein induces an autoimmune reaction in the CNS and sensitized cells and antibodies of a variety of unique specificities. In order to examine the regions of the molecule involved in these immune reactions, fragments of several species of myelin basic proteins (e.g., rat, guinea pig, monkey, bovine) have been prepared by limited peptic digestion and characterized by amino acid analysis, end group analysis, disk gel electrophoresus, tryptic peptide mapping, gel filtration, and chromatography. At least nine fragments have thus far been characterized. Dr. Russell Martenson in collaboration with

Dr. Seymour Levine, Bird S. Coler Hospital, Welfare Island, New York, has examined the encephalitogenicity of the myelin basic protein fragments in the rat, and the peptide known to be encephalitogenic in the guinea pig has no activity in the rat. Of particular interest is the fact that guinea pig basic protein is much more active in the rat than bovine basic protein. Dr. Martenson has been able to narrow down the site of encephalitogenicity of the bovine basic protein in the rat to one region of the polypeptide chain. Similar studies are in progress to determine the encephalitogenic sites for the monkey.

In continuation of his studies of the treatment of EAE with myelin basic protein, Dr. Bernard Driscoll has found that a unique region of the basic protein molecule is required for the induction of antibodies. It is expected that further studies will show that this region is identical with the region known to be capable of inducing EAE in guinea pigs and that it will be identified as the T-cell site. T-cells (thymocytes) are lymphocytes either derived from or influenced during development by cells of thymic origin and are known to be involved in delayed hypersensitivity reactions. They are thought to function as "helper" cells in antibody production and have been implicated as "suppressor" cells in certain types of immune tolerance. An understanding of T-cell specificity in experimental CNS autoimmunity is, therefore, of importance in developing ways of treating patients thought to be affected by pathological autoimmune reactions in the CNS, e.g., patients with multiple sclerosis.

Mrs. Gladys Deibler has continued her investigation of microheterogeneity of myelin basic protein. The different charged components result from at least two reactions, loss of C-terminal arginines by carboxypeptidase B activity and addition of phosphate by phosphokinase activity. The fragments isolated for immunological studies are also being analyzed to determine the location and nature of the phosphate groups present in the whole molecule.

Section on Membrane Chemistry
Louis Sokoloff, Acting Chief

This Section has been pursuing its investigations on the mechanism of the acetylcholine stimulation of phosphatidylinositide turnover in synaptosomes of the cerebral cortex.

Recent developments suggest that cyclic GMP may be the cellular mediator of acetylcholine actions at the cholinergic synapse. This possibility has been under investigation during the past year. The results thus far demonstrate that cyclic GMP does, in fact, stimulate phosphatidylinositol turnover just like acetylcholine. This finding fulfills one of the requirements to validate the hypothesis. Studies are still in progress to determine whether acetylcholine causes cyclic GMP formation. These studies are currently at the stage of the development of a practical method to measure the low concentrations of cyclic GMP which are expected to be involved.

Annual Report of the

Laboratory of General and Comparative Biochemistry

National Institute of Mental Health

Giulio L. Cantoni, Chief

In 1974, we have continued to attempt to cope with the limitation to growth imposed by budgetary restrictions. We have been able to pursue and develop satisfactorily a number of projects while others had to be abandoned or shelved for lack of manpower. It is necessary, therefore, to point out that perhaps the most significant events of the past year were those that did not occur -- the lost opportunities, the squandered leads, the ideas which have not been followed up, the opportunities for fruitful collaboration denied, all because of dwindling support which has now become inadequate to sustain a modern program of investigation even in a relatively circumscribed area of human genetic disease. As one example only, Dr. Mudd's work led us to formulate a working hypothesis as to a possible biochemical etiology for schizophrenia. This hypothesis is described in detail in one of the publications listed in the attached Project Report. However, existing conditions have to date precluded experimental exploration of this working hypothesis. It is, of course, normal in an active research group to develop new projects and to abandon older or less promising lines of research, although it is always more difficult to terminate a project than to initiate one. The difficulties and frustrations are compounded when because of budgetary limitations one has to chose between promising projects.

In 1974, Dr. Cantoni's group has continued to study S-adenosylmethionine analogues and in vitro muscle differentiation. We have had to abandon work on amino acid-tRNA synthetases and our work on ribonuclease H has been limited by the delays with staffing. We are making very good progress in developing the necessary methodology to attack the problem of differentiation of muscle cells in vitro from the biochemical standpoint. We have developed a number of clonal myoblast cell lines differing in their ability to undergo fusion and are in the process of characterizing these lines biochemically and biologically.

Work on S-adenosylmethionine analogues is progressing satisfactorily. We have developed adequate methodology to investigate the effects of S-adenosylmethionine and adenosylhomocysteine analogues on adenosylmethionine synthesis, methyl transfer reactions from adenosylmethionine and the cleavage of adenosylhomocysteine and the study should produce some interesting results.

Dr. Klee has in the past year shifted his major research effort to the study of narcotic drug-receptor interactions. After developing the necessary techniques for demonstrating the presence of narcotic receptors in brain homogenates, we have applied these methods to a number of problems. Morphine dependence, induced in rats by pellet implantation was shown not to cause an appreciable change in the number of narcotic receptors or in their specificity for a series of opiate drugs. In collaboration with Drs. Everette May and Arthur Jacobson, we are studying the interaction of a large number of natural and synthetic narcotic drugs with the morphine receptor. These studies are providing insight into those structural features of narcotics which are critical to receptor interactions as well as those which may be more important features of drug transport and metabolism. In collaboration with Dr. Marshall Nirenberg, a program of screening a number of clonal cells of neural origin, which are maintained in tissue culture, has been carried out. This project has led to the identification of a neuroblastoma-glia hybrid cell line which carries large numbers of specific narcotic receptors on its cell surface. This cell line provides, for the first time, a uniform population of cells which has morphine receptors and which can be used to elucidate the mechanism by which such drugs act. It is already clear that one of the actions of morphine on these cells is to markedly reduce the rate of production of cyclic AMP after stimulation by prostaglandins of the E type. This observation is being actively studied as are other effects of narcotics on these cells, such as those on their electrophysiological properties. Other aspects of this problem which are currently being pursued include efforts aimed at purification of the narcotic receptor and studies of natural constituents of the brain which interact with the receptor.

Dr. K. S. Iyer left the laboratory to return to India in the fall of last year. His studies on the chemical modification of α-lactalbumin and on the thermodynamics of the interaction of α-lactalbumin and the A-protein of lactose synthetase are completed and are being prepared for publication. The results of his work have provided new insights into this interacting protein system as well as some generally useful methodology.

Dr. Merril's group has continued to study the biochemistry of galactosemia. The initial observation that the gene for galactose transferase, carried by the bacterial virus λpgal, can function in the human galactosemic cell line CCL-72 has been extended to three additional galactosemic human cell lines, GM52, GM53 and GM54. These observations indicate that the original results were not unique to a single galactosemic cell line.

Work on the galactosemic cell lines has revealed that the formation of galactose-1-P is required for the "alternate metabolic routes" as well as the Leloir pathway. These studies also revealed that a rapid method of detecting galactosemic fetuses developed by Hill and Puck is not specific for galactosemia as they had hoped.

Their method was based on an attempt to metabolically block the "alternate metabolic routes" for galactose metabolism with galactone. Our studies have shown that the galactolactone becomes galactonic acid under the conditions of their assay and the inhibition is due to a non-specific pH effect.

Bacterial viruses were also injected into whole animals to determine some of the parameters involved in attempts at gene and/or enzyme therapy for metabolic errors in mammals. These studies revealed that the spleen is capable of non-destructively trapping whole virus particles. This trapping ability may allow the spleen to serve as a reservoir of antigen. Such a reservoir may be necessary to elicit an immune response when an animal receives a single antigen challenge.

The past year has witnessed the completion for publication of several major projects within the Section on Alkaloid Biosynthesis. The experimental evidence supporting the role of O-phosphohomoserine as the major homoserine ester formed by green plant extracts, present in green plants, and serving as substrate for cystathionine formation by green plants has been completed. A sensitive and specific method for assay of cystathionine has been developed and usefully applied to green plants. Development of techniques for growth of the single-celled alga, Chlorella, in a chemostat in a steady-state condition with severely limited sulfate has laid the groundwork for a new major project aimed at gaining definitive evidence as to pathways of sulfur amino acid formation in plants. In the area of metabolic disease, evidence has been obtained which rather conclusively establishes the importance of small residual enzyme activities in human patients, and the therapeutic potential of enhancement of such activities. It has been found that in cystathionine synthase deficiency a small increase in the enzyme activity from 0.5-2% of normal to 4 or 5% of normal is adequate to correct the biochemical defect.

It is difficult to overemphasize the importance of these findings. The therapeutic management of many genetically determined metabolic diseases appeared hopelessly hampered by the realization that most patients suffering from genetic diseases with well characterized biochemical defects exhibit only traces of the defective enzyme activity (1-2%) when compared to normal. It was thought for many years that enzyme replacement therapy of one kind or another would prove to be immensely difficult because of the "presumed" need to replace the missing enzyme activity virtually in its entirety. The discovery that it is sufficient to change the small residual enzyme activity by a relatively small factor introduces a new dimension into the problem.

ANNUAL REPORT OF THE LABORATORY OF NEUROBIOLOGY

NATIONAL INSTITUTE OF MENTAL HEALTH

Ichiji Tasaki, Chief

Experiments in the Laboratory of Neurobiology have concentrated on studying the nervous system at two levels. At the single cell level work has proceeded on elucidating the physicochemical basis of nerve excitation. At the central nervous system level experiments have been done on the organization of cells in the brain related to vision and eye movement.

The extrinsic fluorescence signals in nerve fibers were studied to elucidate the physicochemical basis of nerve excitation. The spectrum of the portion of the fluorescent light deriving from aminonaphthalene-sulfonate compounds incorporated into the axonal membrane was determined with a special high-time resolution spectrofluorometer constructed in this laboratory. The spectrum measured in the resting state of the crab and squid nerve fibers was not very different from that of those fluorochromes bound non-covalently to various commercially available biopolymers (lipids and proteins). The portion of light contributing to a small change in the fluorescence intensity (i.e., to fluorescence spikes) was found to have a very sharp and narrow spectrum which could not be encountered when these fluorochromes were incorporated into any of the biopolymers.

Extensive in vitro studies of the physicochemical factors influencing the intensity of the spectrum of 2-p-toluidinylnaphthalene-6-sulfonate (2,6-TNS) showed the following: (1) The emission spectrum of 2,6-TNS is strongly affected by the solvent polarity, as shown previously by McClure and Edelman. (2) Chemical quenching of 2,6-TNS influences the fluorescence intensity without affecting the emission spectrum. (3) A change in the number of bound 2,6-TNS molecules alters the fluorescence intensity again without being accompanied by a shift in the emission maximum of the spectrum. (4) A change in the viscosity of the medium can affect both the emission spectrum and the fluorescence intensity. Based on the results of these in vitro studies, it was concluded that fluorescence signals in squid and crab nerve fibers are produced by a change in the polarity of the microenvironment around the fluorescent probe molecules in the axon membrane.

In addition to these spectral studies the role of water molecules in the process of nerve excitation was investigated by substituting heavy water in the artificial saline solution; this substitution was found to affect the intensity of the fluorescent light emitted by nerve fibers labelled with 2,6-TNS. It was concluded that there is direct involvement of the water molecules in the process of nerve excitation.

The biochemistry of protein synthesis was studied in the isolated nerve bundles of lobster. Electrophoresis, autoradiography and rate of incorporation of labeled leucine into soluble proteins was determined in order to assess the number of proteins, their activity and localization. The soluble proteins were found to be quite homogeneous electrophoretically from either peripheral,

ganglia or connective. However, the incorporation rate of the average protein varied considerably (60,000 c.p.m./mg protein as compared to 10,000 c.p.m./mg protein).

Experiments on the organization of cells in the central nervous system have concentrated on a comparison of cellular activity in the two major branches of the visual system. The discharge of single brain cells has been recorded in awake monkeys (Macaca mulatta) trained to do several visually related tasks. In the midbrain branch of the visual system, the superior colliculus, cells discharged more vigorously to a visual stimulus as the monkey prepared to make an eye movement to that stimulus. This response enhancement, because it is selectively related to stimuli in one part of the visual field, is a possible neural correlate of selective attention. In the other branch of the visual system, the striate cortex, we have now found that such selective enhancement does not occur. Here eye movements to the visual stimulus occasionally were associated with an enhanced response of the cell, but also with eye movements to all parts of the visual field; this generalized enhancement may be related to level of arousal of the monkey. The tentative picture that emerges from these experiments is that of a division of labor between cerebral cortex and brainstem at these early stages of processing. The cortex does the fine analysis of the stimulus; the brainstem selects and emphasizes which stimulus is important.

To determine whether the selective enhancement seen in the superior colliculus was related to any movement made by the monkey in response to the stimulus, the monkey was required in one set of experiments to respond to the stimulus with his hand but not make an eye movement. The cells in the superior colliculus did not show an enhancement of response with hand movement comparable to that seen with eye movement indicating that the type of response made by the monkey does alter the processing of visual stimuli at a very early stage of the visual system.

How damage of striate cortex and superior colliculus cells would influence the detection of small spots of light and the guidance of rapid eye movements to the small spots of light was also determined. Lesion of the colliculus alone did not alter the detection of spots of light nor, as we have found previously, did the lesion alter significantly the guidance of eye movements to the spot of light. Lesion of striate cortex disrupted both of these functions but the disruption largely disappeared within six weeks. However, if both the striate cortex and the superior colliculus were damaged, the monkey became functionally blind in our tests; he could neither detect a spot nor could he saccade accurately to it. Thus in both of these tasks, the striate cortex and the superior colliculus can act as parallel pathways -- after recovery the presence of either pathway permits the animal to perform the task.

Annual Report of the Laboratory of Neurochemistry

National Institute of Mental Health

Seymour Kaufman, Chief

During the last year there were many significant advances made in the Laboratory of Neurochemistry.

We have made a start in our attempts to exploit the finding of the previous year, that patients with the classical form of phenylketonuria (PKU) have detectable levels of phenylalanine hydroxylase (PAH). This finding opened up the possibility that if this low level of PAH activity could be raised an alternate form of therapy for PKU could be developed.

To explore ways in which PAH activity might be enhanced, a reliable and sensitive method of assaying the enzyme *in vivo* was needed. It was also apparent that if such a method were innocuous, it could also be used as a diagnostic procedure to discriminate between patients with the classical form of PKU and those with a milder variant of the disease such as hyperphenylalaninemia. Early (within the first two weeks of life) discrimination between these two conditions is essential because the former disease is treated by administration of a low phenylalanine diet, whereas in the latter condition, such extreme dietary intervention is not needed. Currently, the only certain way for discriminating between these two conditions is by PAH assays performed on liver biopsy samples.

We have developed an *in vivo* assay for PAH which fulfills the requirements for use in humans, as well as in experimental animals. It is based on the administration of ring-deuterated phenylalanine, the substrate for PAH, to animals or humans. When this phenylalanine is converted in the body to tyrosine, some of the deuterium is released in the tissues and blood in the form of D_2O; the rate of release of D_2O (measured quantitatively by infra red spectroscopy) in the blood is an accurate measure of PAH activity *in vivo*. A prerequisite for the successful development of this *in vivo* assay was the chemical synthesis in this laboratory of the appropriate ring-deuterated phenylalanine, a compound that is not commercially available.

The assay method has been fully validated in extensive tests on experimental animals. It is known, for example, that extracts of livers from male rats have 25% more PAH activity than extracts of livers from female rats. The deuterium release assay was able to detect this difference in activity in whole animals. Since the assay employs the innocuous stable isotope, deuterium, rather

than a radioactive isotope, there is no reason why it cannot be used in humans. We anticipate that if it is successfully applied to humans, liver biopsies for the diagnosis of PKU and hyperphenylalaninemia need never again be resorted to.

As an adjunct to the just described *in vivo* assay for PAH, a second assay method has been developed for use in animals. In this method, liver slices are used and the conversion of C^{14}-labelled phenylalanine to C^{14}-labelled tyrosine is measured. In contrast to tissue extracts, the tissue slice method permits the hydroxylation reaction to be measured without any external supplementation; the hydroxylase utilizes cofactors and ancillary enzymes that are already present in the cell in concentrations that are probably a reasonable reflection of their *in vivo* values.

With the development of these two new procedures, we have available accurate PAH assays at three levels of tissue organization: a) the whole animal (deuterium release assay); b) the relatively intact tissue (slice technique); and c) the tissue extract. We have been using all three methods to explore the possibility of increasing the activity of PAH in rats. Preliminary results, in which the first two methods of assay have been used, indicate that administration of certain synthetic analogues of the pterin cofactor to whole animals can lead to marked enhancement of hepatic PAH activity. So far, the enhancement factor that we have achieved is probably below that which would be needed to have significant therapeutic value in PKU. Although there is no reason to believe so, it is also possible that the mutant form of PAH in PKU patients will not respond as does the normal enzyme to this type of supplementation. Nonetheless, the results obtained to date, are extremely encouraging and we intend to pursue the possibility of obtaining PAH stimulation by cofactor administration with vigour over the next few years.

In the second major research problem of the Laboratory of Neurochemistry, the biochemistry of neurotransmitters, several advances were made. Dopamine-β-hydroxylase, the enzyme first purified and characterized in the Laboratory of Neurochemistry, has been shown to be markedly activated by halide ions such as chloride and bromide. In view of the recent hypothesis that schizophrenia may be caused by a defect in CNS dopamine-β-hydroxylase, the regulation of the activity of this enzyme becomes of special importance.

With another key enzyme involved in neurotransmitter biosynthesis, tyrosine hydroxylase, we have shown that certain phospholipids can activate the purified enzyme. The phospholipid activates by increasing the apparent affinity of the enzyme for its pterin cofactor. Since tyrosine hydroxylase is believed to catalyze the rate limiting step in the biosynthesis of noradrenalin and adrenalin, and since the concentration of the pterin cofactor

in brain appears to be limiting, this activation by phospholipids may be an important regulatory mechanism in controlling the rate of catecholamine biosynthesis.

Tryptophan hydroxylase occupies the analogous position in the serotonin biosynthetic pathway as does tyrosine hydroxylase in the noradrenalin pathway: it is believed to catalyze the rate-limiting step in the synthesis of this putative neurotransmitter. During the last year we have come close to our goal of purifying to homogeneity this important CNS enzyme. The availability of pure tryptophan hydroxylase should allow us to prepare a specific antiserum to the enzyme. The availability of this antiserum should find many applications, e.g., to map serotonergic pathways in the CNS.

In the area of cell membranes, it has been shown that the insulin receptor, which is located in the surface membrane, is under negative feedback control by free insulin: when the concentration of free insulin is high, the concentration of membrane insulin receptors decreases. This finding adds another parameter to our understanding of the normal and pathological interaction of hormones with the cells whose functions these hormones regulate. Thus, the known resistance to insulin of obese mice can now be explained as being due to a decrease in insulin receptors that is caused by the increased concentration of free insulin.

In another major research area of the Laboratory of Neurochemistry, that of the mechanism of DNA-DNA recombination, a highly important advance was made during the last year. For the first time, a system has been developed which allows this fundamental biological process to be studied in the test tube. Using this system, it has been found that DNA-DNA recombination is dependent on energy derived from metabolic processes.

Although the specific recombinational event that is being studied in this in vitro system is the insertion of a piece of viral DNA into the host genome, there are good reasons to believe that the enzymology of this process will be the same as that used for all other modes of DNA-DNA recombination. In other words, it should now be possible to analyze in a cell-free system all of the reactions that are involved in the normal maintenance of genetic integration, as well as those involved in the creation of genetic variability. If the cure of genetic diseases by the route of introduction into the cell of normal genes to replace mutated genes is ever to become a reality, the newly developed in vitro system should provide a rational basis for exploring this possibility.

Annual Report of the Laboratory of Neurophysiology

National Institute of Mental Health

Edward V. Evarts, M.D., Chief

July 1, 1973 -- June 30, 1974

This summary of the research program of the Laboratory of Neurophysiology will describe four areas of ongoing research according to which the projects of the Laboratory may be categorized. Each of these four areas has been subdivided into two sections and the summaries will be organized according to these major areas and their subdivisions.

I. Brain Mechanisms in Motor Control

1. Integration of Major Subsystems
2. Integration of Reflexes and Central Programs

II. Brain Mechanisms in Memory and Attention

1. The Prefrontal Cortex and Short-term Memory
2. Effects of Barbiturates on Attentive Behavior

III. Metabolic Correlates of Activity in Brain and Muscle

1. Neurochemical and Neuroanatomical Correlates of Behavior
2. Muscle Function and Metabolism

IV. Functional Neuroanatomy

1. Transport Mechanisms Across Membranes and the Blood-Brain Barrier
2. Anatomical Analysis of Thalamic Input to the Motor Cortex

I. BRAIN MECHANISMS IN MOTOR CONTROL

1. Integration of Major Subsystems

One of the central goals of current research on brain mechanisms controlling movement is discovery of the way in which information flows between the four major subsystems of the brain's motor control system: 1) the basal ganglia, 2) the cerebellum, 3) the thalamus, 4) the cerebral motor cortex. Each of these structures has long been known to have an important function in motor control, but only now are we coming to understand how the structures are interrelated in control of movement. Understanding of these interrelations has been advanced by our development of techniques which allow the activity of individual neurons to be recorded in the course of normal movement in monkeys, and two of the nine current projects in the Laboratory of Neurophysiology are investigating motor system integration using these techniques.

The first of these two projects deals with the role of cerebral motor cortex in control of movement. In primates, a zone of cerebral cortex lying anterior to the central fissure (precentral motor cortex) contains a set of neurons whose axons pass without interruption to the spinal cord via a nerve bundle named the pyramidal tract; the neurons of this tract are called pyramidal tract neurons (PTNs). In the spinal cord the axon terminals of PTNs end both in the interneuronal pool and on alpha and gamma motoneurons.

In our studies of the functional role of motor cortex PTNs, we have compared their activity with the activity of spinal cord α-motoneurons (α-motoneurons innervate skeletal muscle, whereas γ-motoneurons control the sensitivity of intramuscular stretch receptors). In this comparison we found that while all α-motoneurons are inactive during muscular inactivity, most PTNs are tonically active even during total muscular quiescence. Furthermore, recordings of PTN activity in awake monkeys make it clear that discharge frequencies of PTNs are being modulated and controlled even in the absence of any movement. During the past year we have studied PTN discharge in monkeys who are able to carry out differing movements depending upon the "instructions" they have received. These studies have revealed that one factor influencing motor cortex PTN discharge frequency in the absence of overt muscular contraction is the intention to move. The variation in PTN activity in relation to intention to move is seen even before any muscular activity occurs. Thus, when a monkey has learned that a particular signal (e.g., a red light) means he should flex his elbow, PTNs adopt a pattern of discharge corresponding to the intention to flex. A different pattern of PTN discharge frequency is adopted if the monkey receives a signal (e.g., a green light) instructing him to extend. These patterns of PTN activity, which are specific to the impending movement, occur well in advance of any overt muscular contraction, for in these experiments the monkeys were required to wait several seconds between the instruction telling them what to do and a second signal which told them that the time had come to carry out the instruction. Thus, motor cortex neurons show specific patterns of activity depending not only on a movement which is in progress but also depending upon a movement which is impending.

In the experiment referred to above, the "instruction" (a red or green light) was followed by a second stimulus, which was a signal to the monkey to carry

out the movement. This second stimulus was a perturbation of the handle grasped by the monkey, and such a stimulus activates receptors which send information both to the motor cortex and to the spinal cord. A second striking feature of motor cortex PTN activity which differentiates it from the activity of spinal cord motoneurons is the extent to which the responsiveness of PTNs to such sensory inputs may be modified depending upon the movement which this sensory input will trigger. Thus, the responsiveness of PTNs to incoming sensory stimuli was "gated" on or off depending upon the instruction which the monkey had received and, thus, depending on the movement he intended to make. This gating of PTN responsiveness to sensory inputs allows selectivity of motor behavior depending upon decisions made by the subject. The motor cortex may be thought of as a flexibly controlled center in which input-output relations can be changed.

The Cerebellum, Basal Ganglia, and Thalamus. The anatomical origin of the fibers coming into motor cortex indicates that the activity of motor cortex neurons must depend to a very large extent on the impulses from the cerebellum and the basal ganglia which reach motor cortex via the thalamus. Unlike axons of motor cortex PTNs, axons of cerebellar and basal ganglia neurons do not have direct access to the spinal cord. Their outputs must be relayed synaptically, either via thalamus and motor cortex or via brain stem.

Recordings of activity of single neurons in thalamus, cerebellum, and basal ganglia during movement have now led to reappraisal of former ideas as to the relationship of cerebellum and basal ganglia activity to motor cortex. Formerly, it was believed that the major role of the cerebellum was regulation of movement already in progress, this regulation being based on feedback from muscles after they had begun their contraction. It therefore came as a surprise when we found that changes in cerebellar activity occurred prior to movement. Our studies also revealed that cells of basal ganglia become active prior to movement. The finding that both basal ganglia and cerebellum are active prior to movement has led to a new notion of the functional relation of these two structures to motor cortex. This notion starts from the known anatomical fact that the entire cerebral cortex sends fibers to both the basal ganglia and the cerebellum. The cerebellum and basal ganglia in turn send massive connections back to the cortex, and especially the motor cortex, by way of the thalamus. Thus, the basal ganglia and the cerebellum receive information from the whole brain, transform this information, and then send a new pattern of signals which controls the output of the motor cortex. Rather than being at a lower level of the motor system (i.e., closer to the motoneuron) and operating only to correct motor cortex discharge on the basis of feedback from muscle, both cerebellum and basal ganglia are now seen as structures which send commands to the motor cortex even before the muscles begin to contract.

Having made observations on globus pallidus and cerebellum, we next began investigations of the part of the thalamus (named nucleus ventralis lateralis, or VL) which transmits signals from globus pallidus and cerebellum to motor cortex. In these experiments, the activity of VL neurons was recorded in awake monkeys trained to maintain the handle of a manipulandum within a small zone, despite perturbations to handle, and to perform slow and rapid arm movements triggered by a visual stimulus.

VL units related to arm movement were located within a restricted medio-lateral zone centered at approximately the middle of the nucleus, and neurons in this zone discharged in relation to both slow and rapid arm movements. Thus, VL neurons are unlike one source of its afferents, the globus pallidus, which contains neurons that are preferentially related to slow movements.

Units related to jaw and tongue movements associated with the juice reward were located medial to arm-related units. Concurrent anatomical studies utilizing retrograde transport of horseradish peroxidase indicate that the VL region in which units related to arm movement were recorded projects to the "arm" area of the motor cortex. In addition, microstimulation (<25 μA) in the arm movement-related region of VL evoked contractions of shoulder and forelimb musculature.

Unlike hand area motor cortex neurons, most VL neurons showed little or no change in activity in relation to passive manipulation of arm or hand. Some VL neurons, however, did show short latency (<50 msec) changes in activity following small perturbations of the manipulandum handle held by the monkey. Whether these short latency VL responses reflect sensory driving during task performance or short latency motor responses related to the corrective movements which followed the handle perturbation remains to be determined.

These new findings on VL are important because it is now known that in a number of movement disorders the thalamus plays a prominent role in propagating the abnormal signals of diseased subcortical structures to the motor cortex. For this and other reasons thalamic lesions have been made in human patients for a number of years to reduce the tremor and rigidity accompanying Parkinson's disease. The discovery and use of L-dopa drug therapy has reduced the use of thalamic-lesion treatment; however, many neurologists maintain that the best results are obtained with the combination of both drug therapy and thalamic lesions. Knowledge of VL function should provide a firmer basis for the treatment of brain disorders causing abnormal movements by furthering our understanding of what role the thalamus plays in the control of normal movement.

2. Integration of Reflexes and Central Programs

In addition to investigating coordination between motor control subsystems, we are also seeking to understand how the outputs from these subsystems are "hooked up" with the motor apparatus itself. The brain output must act on motoneurons which directly control muscle, and these motoneurons are also impinged on by direct sensory inputs. These two sorts of inputs mediate "reflex" and "voluntary" movements, and in order to understand control of movement we must understand how these reflex and voluntary controls are coordinated. Our work on the role of the vestibular nuclei in the generation of head and eye movements is aimed at providing information which will advance our understanding in this area. The vestibular nuclei receive sensory information from the labyrinth which accurately describes both the orientation of the head in space and also any rotary motion which it undergoes; this information is needed for the maintenance of body posture and is vitally important in the stabilization of the head and eyes. Experiments were designed to establish whether the vestibular nuclei are solely sensory relay areas mediating reflexes

or whether they also participate directly in the generation of the motor programs which ultimately guide the eyes, head and trunk.

The approach used here involved microelectrode recordings in the vestibular nuclei in conscious monkeys. The results of these experiments make it clear that the activity of many neurons in the vestibular nuclei closely reflects various elements of the oculomotor program under a wide variety of behavioral conditions. This finding strengthens the idea that all eye movement programs are "compiled" in the vestibular nuclei. In addition, it is now evident that even animals whose heads have been habitually immobilized in the experimental situation still attempt some head movements. Such gestures are often tightly coupled to eye movements, and the neural events in the vestibular nuclei often reflect various aspects of such centrally programmed head movements.

The present study also showed that many of the neurons which have classically been called "vestibular" because they seemed to be driven purely by head rotation in a particular direction, also fire when the animal actively attempts to turn its head in the converse direction; this strongly suggests that given neurons in the vestibular nuclei mediate both vestibularly induced and centrally programmed contractions of the neck muscles.

II. BRAIN MECHANISMS IN MEMORY AND ATTENTION

1. The Prefrontal Cortex and Short-term Memory

An improved understanding of the prefrontal cortex has long been a major research goal within a number of different subdisciplines within the field of neuroscience. In particular, research workers in the clinical disciplines of neurology and psychiatry and the experimental disciplines of neurophysiology and psychology have sought to advance knowledge of the function of the prefrontal cerebral cortex in man and subhuman primates. The goal of our current work in this area has been to achieve a more detailed understanding of the organization of the neuronal activity occurring in association with behavioral tasks in which prefrontal cortex is critically involved.

In these studies using subhuman primates, our point of departure comes from the fact that lesions of the prefrontal cortex give rise to marked disturbances in spatial memory. These defects in spatial memory following prefrontal cortex lesions in subhuman primates have been assessed by performance on tasks referred to as "delayed alternation" or "delayed response". In these tasks the monkey subject is required to remember which of two spatially separate locations he should select. For the present study, delayed alternation was used. For such a task the animal is required to depress a central key for a period of several seconds, following which two laterally placed keys become illuminated. The monkey must then select the key he did not select on the previous trial. On successive trials he must select these two laterally placed keys in alternation. Thus, he must first depress the central key and when the laterally placed keys become illuminated he must press the one to the right. He then returns to the central hold key, but the next time the laterally placed keys become illuminated he must press the left key. This task continues for many trials. In association with performance of this task, the

present project involved recording the activity of single nerve cells in prefrontal cortex by means of microelectrodes.

In this work we have found that many neurons in the prefrontal cortex are differentially active during the delay period depending upon whether the selection to follow will be to the right or to the left, demonstrating that activity of prefrontal cortex cells can code the spatial memory which is necessary to guide the monkey's impending motor response. This is the first demonstration of this fact.

Some of these neurons showed clear dependence on the relations between choice keys. This finding on the significance of the relative position of the choice key indicates that an important dimension of coding of spatial memory in prefrontal cortex is the "rightness" or "leftness" of the choice key. This indicates that spatial memory is coded at a rather high level of abstraction in the prefrontal cortex of the primate brain.

The prefrontal cortex is a region of the brain which is a borderland between neurology, psychiatry, neurophysiology, and neuropsychology. The present project has succeeded in revealing certain aspects of the way in which spatial memory is coded in this part of the brain. Much remains to be done in connection with this type of work, but the present work has made a beginning with its discovery that nerve cells in the prefrontal cortex show directional selectivity during a delay period and thus that they may participate in a central mnemonic code for correct spatial choice.

2. Effects of Barbiturates on Attentive Behavior

The overall goal of this research is to understand the central nervous system alternations occurring during impaired attentive behavior. Previous work has investigated behavioral and EEG aspects of impaired attention produced in trained monkey subjects by the administration of secobarbital and chlorpromazine. This work suggested that the mechanism of impairment produced by these two drugs differed; chlorpromazine seemed to produce primarily a phasic blocking of input process subserving arousal. Secobarbital, on the other hand, seemed to suppress the functional level not only of arousal processes but of motor effector mechanisms as well. The present study was designed to focus on these effector mechanisms as they come into play during the performance of a sustained discriminated attention task. The question being investigated is whether and how neuronal activity is altered by centrally-acting drugs during attentive behavior. The methods used permit dissection of two components of the motor behavior: time to initiate the response after the "go" signal has appeared (initiation time) and time to execute the response (movement time).

In these studies it has been found that delays in reaction time caused by secobarbital involve a delay in the arrival of information at motor cortex: once the nerve signals have reached motor cortex, the subsequent steps in the behavioral chain appear to proceed as rapidly as in the control, undrugged animal.

The information obtained from this project is relevant to two questions of interest to the Institute. 1) The symptom of attention impairment is prominent

in several diseases of largely unknown pathophysiology, i.e., schizophrenia and petit mal epilepsy. Further, it is a commonly observed characteristic of hyperkinetic children. Any information concerning alterations in central nervous system activity during impaired attention should aid in the understanding of the possible brain pathology which is associated with these clinical problems. 2) Although heroin abuse receives more attention, barbiturate abuse is probably more widespread and more dangerous from a physiological point of view. Information concerning the neural effects of barbiturates and related compounds is needed to aid in the comprehension of this problem.

III. METABOLIC CORRELATES OF ACTIVITY IN BRAIN AND MUSCLE

1. Neurochemical and Neuroanatomical Correlates of Behavior

Within recent years advances in neuroanatomical techniques have made it possible to examine the role of brain cells in ways that promise rapid progress in our understanding of brain and behavior. Our work in this area is aimed at obtaining neurochemical and neuroanatomical correlates of central nervous system activity occurring in association with behavior. Such information could provide valuable correlates for the microelectrode techniques in use in the Laboratory. Microelectrode techniques are limited because they selectively record activity from a small set of large cells. Ideally, chemical changes of smaller neurons, neuronal processes, and glia should eventually be related to a behavioral state.

To implement the above objectives we will use an autoradiographic technique in which radioactive deozyglucose is used as an indicator of glucose uptake of localized cerebral regions. Behavioral changes will be correlated to regional changes in glucose uptake. This shows anatomical localization of metabolically active areas and cells, interrelationships between active and inactive areas, and provides basic biochemical data on cerebral metabolism.

Our experiments do suggest the techniques will provide valuable correlates of behavior. Stimulation of the sciatic nerve in anesthetized rats increased the glucose uptake in one dorsal horn of the spinal cord several times the control side. In these experiments it was seen that most, if not all, elements of the central nervous system take up glucose but the exact proportions to assign to each await improvement in the technique. In addition, it has been found that the metabolic rate of the central nervous system of the swimming rat is significantly increased over the resting control rat.

This work provides a different approach to investigating the central nervous system, one which will open new vistas into brain function and possible malfunction. The techniques are designed to give an index of activity and to be correlated to behavioral, pathologic, and phamracologic states of the central nervous system. The project would provide an eventual link between the Laboratories of Cerebral Metabolism, Neurophysiology, and Neuropharmacology.

2. Muscle Function and Metabolism

The relations in muscle among metabolism, regulation of ionic homeostasis, and contraction are not understood clearly. The interaction among these fundamental

mechanisms is important to the comprehension of basic muscle physiology and the more complicated analysis of muscle disease and disorders of movement.

We have shown that (a) mechanical properties of muscle (stretch) regulate contractility and ionic contents, probably by stimulating metabolism and the sodium-potassium exchange pump, and (b) metabolism in turn regulates twitch and tetanus in single fibers. Fatigue is evident at the level of contraction of the excitation-contraction process in muscle. It is now possible to construct a more meaningful feedback relationship between metabolism, ionic content, and muscle contraction.

IV. FUNCTIONAL NEUROANATOMY

1. Transport Mechanisms Across Membranes and the Blood-Brain Barrier

The action of drugs and hormones on the brain depends in large measure on their entrance into nervous tissue from the blood, and this passage involves crossing a system referred to as the "blood-brain barrier". For several years, a major research effort in our Laboratory has sought to understand the nature and function of the blood-brain barrier, and to amplify the theory of active and passive transport across cellular membranes.

In this work it has been found that osmotically concentrated solutions have the capacity to "open" the blood-brain barrier. The blood-brain barrier regulates exchange of materials between blood and brain and therefore controls brain metabolism and is important in brain pharmacology, since some drugs are excluded by it from entering the brain. Our finding of osmotic barrier opening is the first demonstration of a reversible opening that is based on morphology and simple physical-chemical laws applicable to cells in general. It will permit experimental modification of the blood-brain barrier for studying brain metabolism and perhaps for brain pharmacology. The theory of osmotic opening can be used to interpret regulatory functions of the barrier, and to understand how diseases associated with plasma hypertonicity can modify the barrier and produce clinical symptoms. These diseases include, for example, diabetic acidosis associated with coma.

Our findings also have significance for x-ray diagnosis of neurological disorders in man. X-ray contrast media are injected into the carotid artery to visualize the cerebrovascular tree for clinical disorders of the brain. There is a significant morbidity and mortality associated with the technique, yet the factors affecting neurotoxicity are poorly understood. Our work shows that (a) these agents can and probably do open the blood-brain barrier because of their high osmolality, and (b) that even if they do not open the barrier, they can enter the brain and affect neurons by virtue of their lipid solubility properties. This is the first time that neurotoxicity of x-ray contrast media is considered in terms of simple physical-chemical laws of osmosis and cell membrane permeability, and it would be hoped that less toxic contrast media (with lower osmolalities and lipid solubilities) will be synthesized in the future. On the basis of the relation between lipid solubility and neurotoxicity, we have been able to suggest a series of compounds which should be less neurotoxic than any in current use and should reduce the incidence of untoward effects in cerebral and spinal cord angiography.

2. Anatomical Analysis of Thalamic Input to the Motor Cortex

A second phase of our work in functional neuroanatomy is aimed at anatomically determining which regions of the thalamus influence the motor cortex and how the connections between thalamus and cortex are functionally organized. This study utilizes the phenomenon of "axon flow" to label pathways going into or out of the motor cortex. Radioactive labeled amino acids injected into the motor cortex are taken up and incorporated into proteins at the cell bodies of motor cortex neurons. These proteins are then transported from the cell body, down the axon, to their synaptic terminals (orthograde axonal flow). When the tissue is processed by autoradiographic methods, labeled proteins appearing in axons and synaptic terminals of motor cortex output pathways are visualized.

Low molecular weight proteins injected into the motor cortex are taken up by synaptic terminals in the motor cortex. These proteins are then transported from the terminals, up the axon, back to the cell body (retrograde axonal flow). When the tissue is processed by the appropriate histochemical methods, the protein appearing in cells which send their axons to the motor cortex is visualized. Using the horseradish peroxidase technique, we have successfully labeled the "arm area" of the thalamus, or more correctly, the region of the thalamus which sends fibers to the arm area of the motor cortex.

Neurons which send fibers to the arm area of the motor cortex occurred within a restricted region of VL. Thalamocortical neurons were most concentrated at anterior 8.5, where they formed a "slab" of neurons, 6 mm long in the dorso-ventral direction and 1-1/2 mm wide. The thalamic region which projects to the motor cortex did not also project to the sensory cortex, since no labeled neurons were found in VL following injections of protein into the sensory cortex of another set of animals.

These findings are important because the ventrolateral nucleus of the thalamus (VL) is the primary source of thalamic fibers to the motor cortex. Physiological studies indicate that the type of information the motor cortex receives is determined to a great extent by the input from VL and thus the connection between VL and the motor cortex is a very important one. There is little information, however, about the anatomical organization of VL fibers through which the VL influence on the cortex is exerted. The present findings are important because they outline a discrete anatomical system which plays an important role in controlling the information presented to the motor cortex and thus movement in general. The thalamus has been and will continue to be studied intensively with physiological methods. In trying to understand movement programming in the motor cortex and in the "motor" thalamus, it will be most important to compare regions of both structures which are interconnected. The present studies indicate which are the relevant thalamic regions and provide a miniature road map for their localization.

Annual Report of the Section on Technical Development

National Institute of Mental Health

National Institute of Neurological Diseases and Stroke

July 1, 1973 - June 30, 1974

Theodore R. Colburn, Ph.D., Chief

The Section on Technical Development is a group of engineers, computer scientists, and technicians which provides technical services to the Intramural Research Programs of NIMH and NINDS. The major functions of the Section are:

(1) Instrumentation research and development. Design and development of instruments and instrumentation systems which represent advances in the state-of-the-art. Most of the research within the Section falls in this category, and is generally done in collaboration with investigators in the laboratories of NIMH and NINDS.

(2) Production of custom instrumentation. Design and fabrication of electronic, mechanical, and optical equipment to suit the particular needs of the requesting investigator. These instruments, while often quite complex, utilize rather than advance the current state-of-the-art design techniques and components.

(3) Computational services. The Section assists the investigators in data collection, reduction, and analysis, by supporting three laboratory-size digital computers for general use, a medium size time-shared digital computer (SEL 810B) for real-time on-line applications, and by providing programming service and technical consultation.

Additional services provided by the Section include consultation on: measurement techniques; signal processing; noise and electro-magnetic interference in data measurement systems; and equipment purchases. Several formal and informal courses for investigators are taught by Section personnel; topics include electrical circuit theory, operational amplifier applications, digital logic design, and computer applications.

Due to manpower limitations and economic considerations, the Section is unable to provide the following services: repair of commercial instruments, duplication of off-the-shelf commercially available equipment, and fabrication of non-instrument items (shelves, bookcases, etc.).

INSTRUMENTATION

Following are selected instrumentation projects completed by the Section during the past year. These are chosen from a total of 194 projects, many of which consisted of routine fabrication of electronic circuits and mechanical devices.

(1) Telemetry System for Monitoring Patient Movement. A system was developed to monitor the activity of subjects remotely as they move freely within a clinical ward. The detector is built in the form of a wristwatch, and movement of the subject's arm causes a ball bearing to roll in a circular raceway and change the frequency of transmission. The amount of change is proportional to the intensity and rate of subject movement. The transmitted signal is received on antennas distributed around the ward, demodulated, and compared to an adjustable threshold. If the subject's motion is sufficiently intense, a standard pulse is produced which indicates one unit of motion. These pulses are counted and totaled every 10 minutes. The totals give an indication of the subject's daily activity cycle.

(2) Poolesville Rat Colony Data Acquisition System. This system has the capacity to collect, format, and store on tape, in real-time, data from 512 digital input channels. Data is in the form of (a) rat lever-pressing epochs, and (b) a digital number representing the identification of a particular rat passing a particular sensor, and its direction of movement. The system incorporates a computer, tape recorder, and extensive digital logic. The various I/O handler and driver software for the system's peripheral devices were also developed by the Section, as was a software package to model system operation in real-time.

(3) Instrumentation for Acupuncture Research. A stimulator was developed to deliver bipolar rectangular current pulses through acupuncture needles. The amplitude and frequency of the pulses are adjustable, and buffered outputs allow identical current pulses to be passed through ten needles. Currently being developed is a skin impedance mapping device for the location of acupuncture points. Numerous wire electrodes are placed in contact with the skin, and the impedance between each and a reference electrode is measured, to test the theory that acupuncture sites have lower impedance than immediately adjacent points.

(4) EMG Biofeedback System. This instrument allows a subject to learn to relax specific muscles by using the technique of biofeedback. The subject applies skin electrodes and the electrical activity of the selected muscle modulates the amplitude and frequency of an audio tone. The modulating voltage, proportional to the rectified, filtered EMG, is also displayed on a meter, giving the subject both auditory and visual feedback.

(5) Isometric and Isotonic Reflex Measuring System. This apparatus was developed to allow the measurement of the Tonic Vibration Response (TVR)

of the triceps surae muscle group in human subjects. This response is elicited by mechanical vibration of the Achilles tendon and the resulting plantar flexion is measured isometrically by recording the force developed against a stationary footplate or isotonically by recording the amount of rotation about the ankle joint while moving against a constant force. Both prone and supine subject positions may be used.

Owing to its versatility, this apparatus will be used to measure the TVR before, during, and following the implantation of a cerebellar stimulator in human epileptic patients. The measured responses will be used to study the effect of cerebellar stimulation on mono- and polysynaptic reflex pathways at the spinal cord and brainstem level.

(6) Amplitude and Time Window Discriminator. This instrument was developed to detect specific neurophysiological signals in the presence of noise and other signals. For discrimination, a signal must remain between an upper and a lower amplitude bound for longer than a specified minimum time, but less than a maximum time. Use of the two-dimensional window results in greater noise reduction and more accurate discrimination. A multiplexing system allows the data signal, the two amplitude window levels, and the discriminated pulse to be displayed simultaneously on a single oscilloscope beam.

(7) Ion-Sensitive Electrode Amplifier System. The system is comprised of two instruments: an ultra-high input impedance amplifier and filter combination for use with ion-sensitive electrodes; and an ion activity computer which generates the antilog of the amplifier output and gives an output proportional to ion activity over the range 1mM to 10mM.

(8) Infant Motion Detector. This apparatus automatically records infant arm-reaching and leg kicks in a mother-infant mutual learning study. Two infrared light source-detector pairs are mounted on adjustable parallel arms; when infant motion breaks a light beam, a binary signal is generated. Infrared sources were used to avoid distracting the infant with visible light. Focusing at the source and detector allows a separation of five feet, thus keeping the apparatus beyond the infant's reach.

COMPUTER SERVICES

The following table shows the utilization of laboratory computers.

	NIMH	NINDS	NICHD	TOTAL HOURS
MicroLINC-300	64%	36%	--	1408
PDP-12	17%	77%	6%	3428

The unusually heavy utilization of the PDP-12 was a result of the Applied Neurological Research Branch, C&FR using the computer evenings and

weekends. New programming techniques have made the PDP-12 easier to use and the anticipated work load will remain high, even after delivery of ANR's new computer.

The prime users of the microLINC have converted to their own computer systems and potential new applications are being evaluated. The Classic LINC has become unreliable, and as a result, was used less than 200 hours; it will be surplused as soon as is practical.

The SEL 810B computer installation in Bldg. 10 continues to operate reliably, routinely supporting three or four simultaneous users in on-line research applications. Support for this installation is now limited to a routine level of one man year for the systems programmer and less than one-half man year for new interface requirements.

ESTIMATED SEL 810B UTILIZATION

	Total Hours
Laboratory of Psychology, NIMH	
Section on Higher Thought Process	400
Section on Perception	50
Unit on Psychophysiology	1250
Adult Psychiatry Branch, NIMH	
Section on Psychiatric Assessment	150
Section on Experimental Group and Family Studies	100
Section on Perceptual and Cognitive Studies	1500
Laboratory of Clinical Psychobiology, NIMH	
Section on Comparative Studies	150
Laboratory of Socio-environmental Studies, NIMH	
Section on Personality and Environment	175
System Development	200
TOTAL	3975

ENGINEERING AND FABRICATION

The final table shows the distribution of the Section's workload among the various laboratories.

LABORATORY OR BRANCH	HOURS	PERCENT
Adult Psychiatry, NIMH	3411	12.2
Brain Evolution & Behavior, NIMH	2979	10.66
Psychology, NIMH	2814	10.07
Neurophysiology, NINDS	2450	8.77
NIMH 810B Computer	2354	8.42
Neuropharmocology, St. E's, NIMH	2004	7.17
Clinical Science, NIMH	1636	5.85
Behavioral Biology, NICHD	1328	4.75
Biophysics, NINDS	1045	3.74
Molecular Biology, NINDS	897	3.21
Technical Development, NIMH/NINDS	868	3.10
Clinical Psychobiology, NIMH	776	2.77
Neurobiology, NIMH	764	2.73
Surgical Neurology, NINDS	749	2.68
Neurophysiology, NIMH	719	2.57
Neural Control, NINDS	508	1.82
Neurochemistry, NINDS	468	1.67
General & Comparative Biochemistry, NIMH	402	1.43
Neuropathology & Neuroanatomical Sciences, NINDS	362	1.29
Experimental Neurology, NINDS	347	1.24
Collaborative & Field Research, NINDS	290	1.03
Neurochemistry, NIMH	213	.76
Electroencephalography, NINDS	145	.51
All Other Labs	400	1.43
NIMH (Total)	18,506	66.23
NINDS (Total)	8,108	29.02
NICHD (Total)#	1,328	4.75
TOTAL*	27,942	100.0

*The time of the Section Chief is not included in the foregoing totals.

#NICHD loans the Section one position, and is thus entitled to 2000 hours of service.

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